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High-dose escalation and dose intensity are known factors for eradication of tumors and possibly overcoming of drug resistance in breast cancer chemotherapy. During the past year, we evaluated the ability of swainsonine to confer protection against lethality associated with high-dose sequential administration of doxorubicin before high-dose combination of cyclophophamide (CPM)- methotrexate (MTX)- 5-fluorouracil (5-FU) [CMF]. During the administration of four sequential doses of LD_{10} DOX, SW conferred protection against lethality and prolonged survival of mice to a significant extent compared to mice treated with the plain vehicle, PBS. SW administration facilitated and stimulated bone marrow cells and bone marrow colony forming units. Also SW treatments facilitated recovery of mice from neutropenia. The major problem encountered were the loss of entire control mice following the injection of the fourth LD_{10} DOX. Clearly these treatments were too severe for the experimental control mice. In order to get some of these controls to the first CMF combination treatment, no more than three treatments with DOX will be applied in subsequent studies. Furthermore, it is possible that the lethality observed in SW groups after 3rd and 4th LD_{10} DOX may be due to other organ toxicities.

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FOREWORD

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Date

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ACRONYMS AND SYMBOL DEFINITION

BM.....Bone marrow
CFU.....Colony forming unit
CPM.....Cyclophosphamide
DOX.....Doxorubicin
5-FU.....5-Fluorouracil
LD.....Lethal dose
MTX.....Methotrexate
SW.....Swainsonine

PROGRESS REPORT

Introduction:

In the sequential-combination chemotherapy of the Milan breast cancer program, patients received four cycles of DOX (75 mg/m^2 every 3 weeks) followed by eight courses of combination of CPM (600 mg/m^2)- MTX (40 mg/m^2) - 5-FU (600 mg/m^2) every four weeks. In the experiments that are proposed in this application, the emphasis is on determining whether swainsonine (SW) will confer protection at intensed and high doses that are significantly greater than those currently in clinical use. Without absolute drug resistance, increasing the dose and its intensity should increase the log kill and improve results. Since many tumors have a steep-dose response, the current thinking is that drug resistance can be overcome to some extent by high-dose escalation. The experimental support for steep-dose response curves is derived from model systems in which a small increase in drug dose results in a disproportionately large increase in tumor cell kill. In many experimental animal systems, the log kill will be greater for the higher dose intensity drug(s) because that log kill is the difference between cell death and tumor regrowth. Therefore experiments that were carried out during the first year were aimed at assessing the potential usefulness of SW in intensive high-dose escalations using the sequential DOX - CMF combination approach but <u>not</u> simulating the current clinical doses. The limit of protection was also assessed under the experimental conditions described below.

In our previous studies not related to this grant application, we established, following several repeated experiments, the LD_{10} for DOX, CPM, 5-FU and MTX using large numbers of female syngeneic, pathogen-free C57BL/6 mice. These are 11.8 mg/kg, 430.0 mg/kg, 165.0 mg/kg and 185.0 mg/kg body wt, ip, respectively. The degree of lethality of these dosages are reproducibly accurate. These dosages are intended to be used and studied in this funded grant. These dosages are significantly greater than those currently in clinical use for the treatment of advanced breast cancer, for example, 430 mg/kg CPM is equivalent to 1,425 mg/m^2 human and 185 mg/kg MTX is equivalent to 612 mg/m^2 human.

Body:

Before embarking on a large scale experiment, a small pilot study comprising of two groups of mice was carried out first to have an idea on the degree or extent of lethality. One group (Group A) consisted of 60 mice which received SW pretreatments (10 ug/20 gm body wt, BID, ip) for 10 consecutive days, i.e., from day -10 to day -1, followed by an LD_{10} DOX ip injection on day 0, left alone for 7 days, then injected a second LD_{10} DOX on day +8, then left alone for another 7 days and followed by a third LD_{10} DOX on day +16, left alone for 7 days, then given a fourth LD_{10} DOX on day +24, left alone for 7 days before a fifth LD_{10} DOX on day +32. Following these treatments, it was intended that these animals will be left alone for 21 days before receiving a combination of LD_{10} of CPM, 5-FU and MTX, ip, on day +53. Forty-eight hours following this first combination treatment, these animals will start receiving SW (10 ug BID, ip) for 10 consecutive days. All daily SW treatments will be spaced 8 hours apart. At the end of these SW treatments, the mice will be left alone for 15 days before receiving a second combination of LD_{10} of CPM, 5-FU and MTX, ip, on day +79. Forty-eight hours following the second combination, the mice will start receiving SW 10 ug BID, ip, for 10 consecutive days which will end on day +90. At this point the animals will be left alone for additional 15 days. The other group of 60 mice (Group B) was similarly treated except they were pretreated with the plain vehicle, PBS (100

μl/20 gm body wt, BID, ip, for 10 consecutive days, from day -10 to day -1) instead of SW and were also proposed to receive PBS treatment for 10 consecutive days from day +55 to day +64, and for another 10 consecutive days from day +81 to day +90. It was intended that these mice will also be left alone for additional 15 days before terminating the study. Survival of mice was monitored daily in both groups throughout the course of the study. But the study did not progress to the end as originally described because none of the control mice in group B survived beyond the fifth LD_{10} DOX injection. By day +45 (day 55 of the study), the percent survival of mice in group B was 0% while 60% of mice in group A (SW pretreated group) were still alive. Forty-three percent of mice in group A were alive on day +60 when the pilot study was terminated. These observations were schematically summarized in Figure 1. From this pilot study it was clear to us that the treatment intensity was too much to bear for PBS treated (control) mice. Therefore a therapeutic strategy that will maintain the same dosage of DOX but an adequate period for recovery in between the DOX treatments will be needed. In the five sequential DOX treatments carried out in the pilot study, one SW or PBS pretreatment for ten consecutive days was used. Then the immediate question posed was what was the limit of effects of one SW pretreatment for 10 consecutive days on the bone marrow (BM) and on the hematologic parameters of interest. Knowledge gained from this would let us know how long we can allow the mice to rest in between the DOX injections based on one pretreatment. Data obtained from this study showed that one SW pretreatment for 10 consecutive days significantly increased all parameters of interest up to day +60 (which was actually day 70) of study. These findings are summarized in Figures 2a-2g and 3a-3g. Upon the basis of these findings, a major survival study and assessment of effects on BM and hematologic parameters were undertaken. This study was carried out as follows. Mice were stratified into three groups. Group I was the normal controls that received only the plain vehicles. Group II mice were the experimental controls that were treated with PBS and DOX. Group III mice received SW and DOX treatments. Groups II and III mice received the following treatment protocols. Mice in Group II were pretreated with PBS from day -10 to day -1 and were injected LD_{10} DOX on day 0 (which was day 11 of study); on day +15 which was day 26 of study, each surviving mouse was injected another LD_{10} DOX. This injection was followed by another injection of LD_{10} DOX into each surviving mouse on day +30 which was day 40 of the study. Then each surviving mouse was treated with another cycle of PBS treatment for ten consecutive days beginning on day +45 up to day +54, that is, from day 55 to day 64 of study. This treatment cycle was then followed by the injection of the fourth LD_{10} DOX into each surviving mouse on day +55 which was day 65 of the study. These mice (Group II) were monitored daily for survival study and also were worked upon for BM and hematologic studies. Group III mice received treatment protocols similar to those in Group II except that Group III mice were pretreated with SW 10 μg BID from day -10 to day -1 and had another SW treatment cycle for ten consecutive days from day +45 to day +54. Mice in Groups I and III were monitored daily for survival studies and were worked upon for BM and hematologic studies on the same day intervals as those in Group II. Results from these studies are summarized in Figures 4, 4-continued, and 4a-5I. SW treatments conferred protection against lethality and prolonged survival of mice. On day +66, there was zero percent survival of mice in Group II while 100% and 40% survival were noted in Groups I and III respectively. On day +70, 30% survival were observed in Group III and 100% in Group I. SW treatment facilitated and stimulated BM and BM CFUs. Also SW treatment facilitated recovery of mice from neutropenia. It is conceivable that the lethality observed in Group III may be due to other organ toxicities. Histopathologic evaluations of tissues collected will answer this possibility in

near future.

Impact on SOW:

From these experiments, it is clear that these treatments were too severe for the experimental control mice. In order to get some of these controls to the first methotrexate-5-FU-cyclophosphamide treatment, no more than three treatments with DOX will be applied in subsequent studies. Furthermore, experience gained so far has necessitated taking the following treatment protocols. Mice will be pretreated for 10 consecutive days either with SW or PBS from day -10 to day -1, then on day 0 will receive the first LD_{10} DOX and the second LD_{10} DOX will be given on day +8. Next on day +29, the animals will receive another treatment cycle with SW or PBS for 10 concencutive days and then injected a third LD_{10} DOX on day +39. On day +69, the mice will receive the first combination treatment with methotrexate-5-FU-cyclophosphamide. This approach will help sustain some control mice into the first combination treatment.

Abstract:

High-dose escalation and dose intensity are known factors for eradication of tumors and possibly overcoming of drug resistance in breast cancer chemotherapy. During the past year, we evaluated the ability of swainsonine to confer protection against lethality associated with high-dose sequential administration of doxorubicin before high-dose combination of cyclophophamide (CPM)- methotrexate (MTX)- 5-fluorouracil (5-FU) [CMF]. During the administration of four sequential doses of LD_{10} DOX, SW conferred protection against lethality and prolonged survival of mice to a significant extent compared to mice treated with the plain vehicle, PBS. SW administration facilitated and stimulated bone marrow cells and bone marrow colony forming units. Also SW treatments facilitated recovery of mice from neutropenia. The major problem encountered were the loss of entire control mice following the injection of the fourth LD_{10} DOX. Clearly these treatments were too severe for the experimental control mice. In order to get some of these controls to the first CMF combination treatment, no more than three treatments with DOX will be applied in subsequent studies. Furthermore, it is possible that the lethality observed in SW groups after 3^{rd} and 4^{th} LD_{10} DOX may be due to other organ toxicities.

Survival of Mice during Chemotherap
Pilot Studies

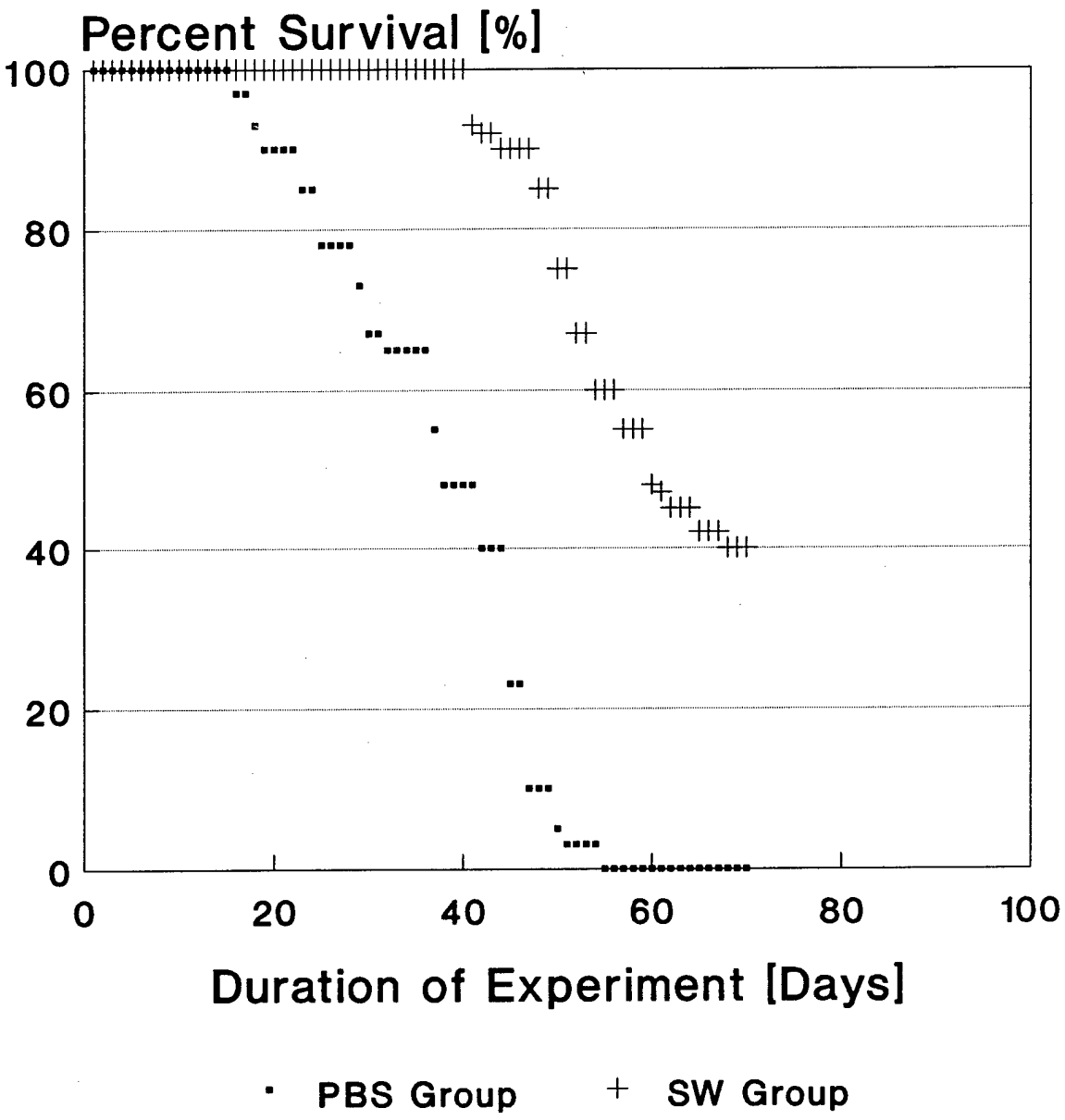

Figure 1
Mice in both groups were injected LD10 DOX on days 11, 19, 27, 35 and 43.

Assessment of Duration of Effects of SW

Effects of SW on BM and Hematologic Parameters During SW Treatment

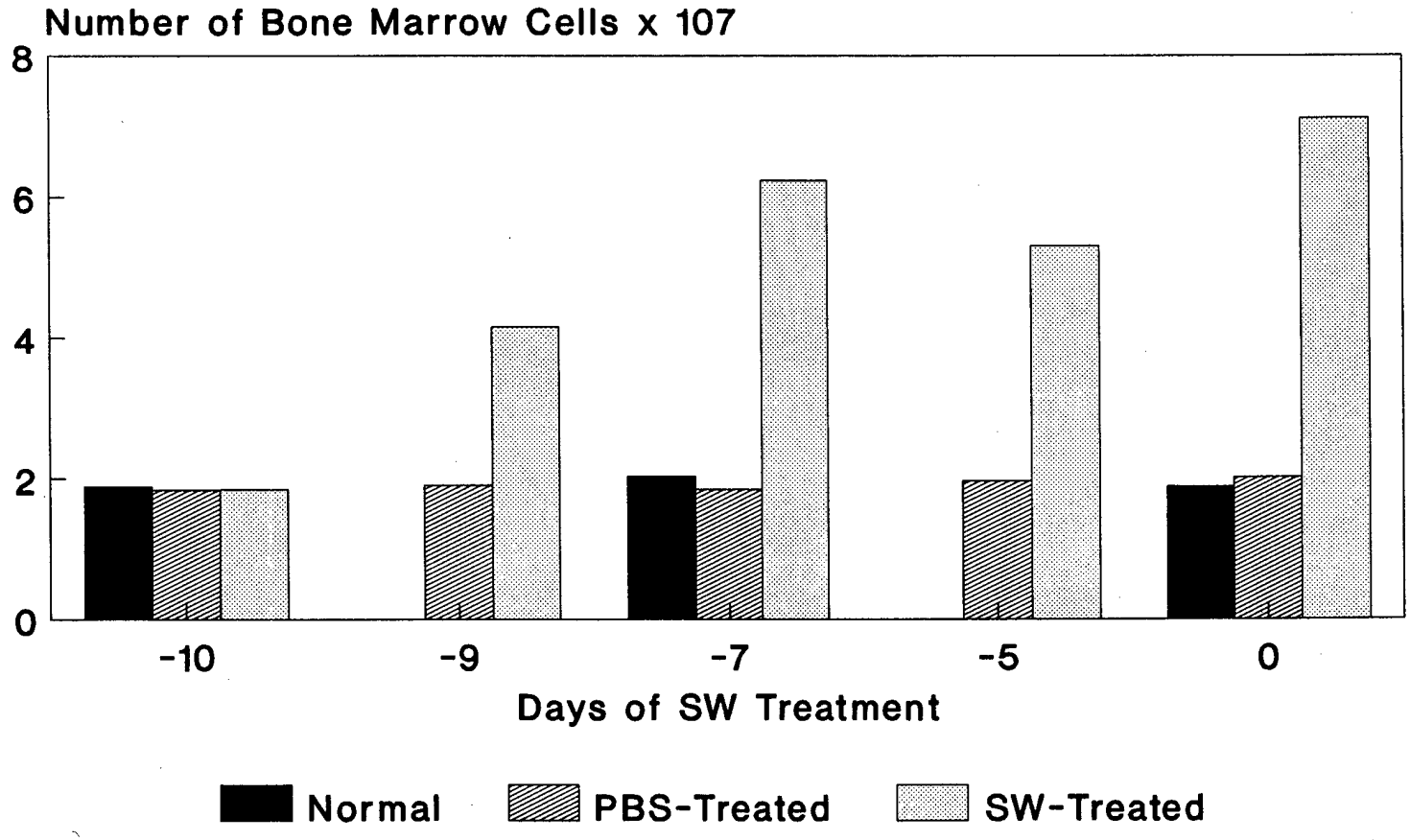

Figure 2a - BM Cellularity During SW Treatment; BM = Bone Marrow

Assessment of Duration of Effects of SW

Effects of SW on BM and Hematologic Parameters During SW Treatment

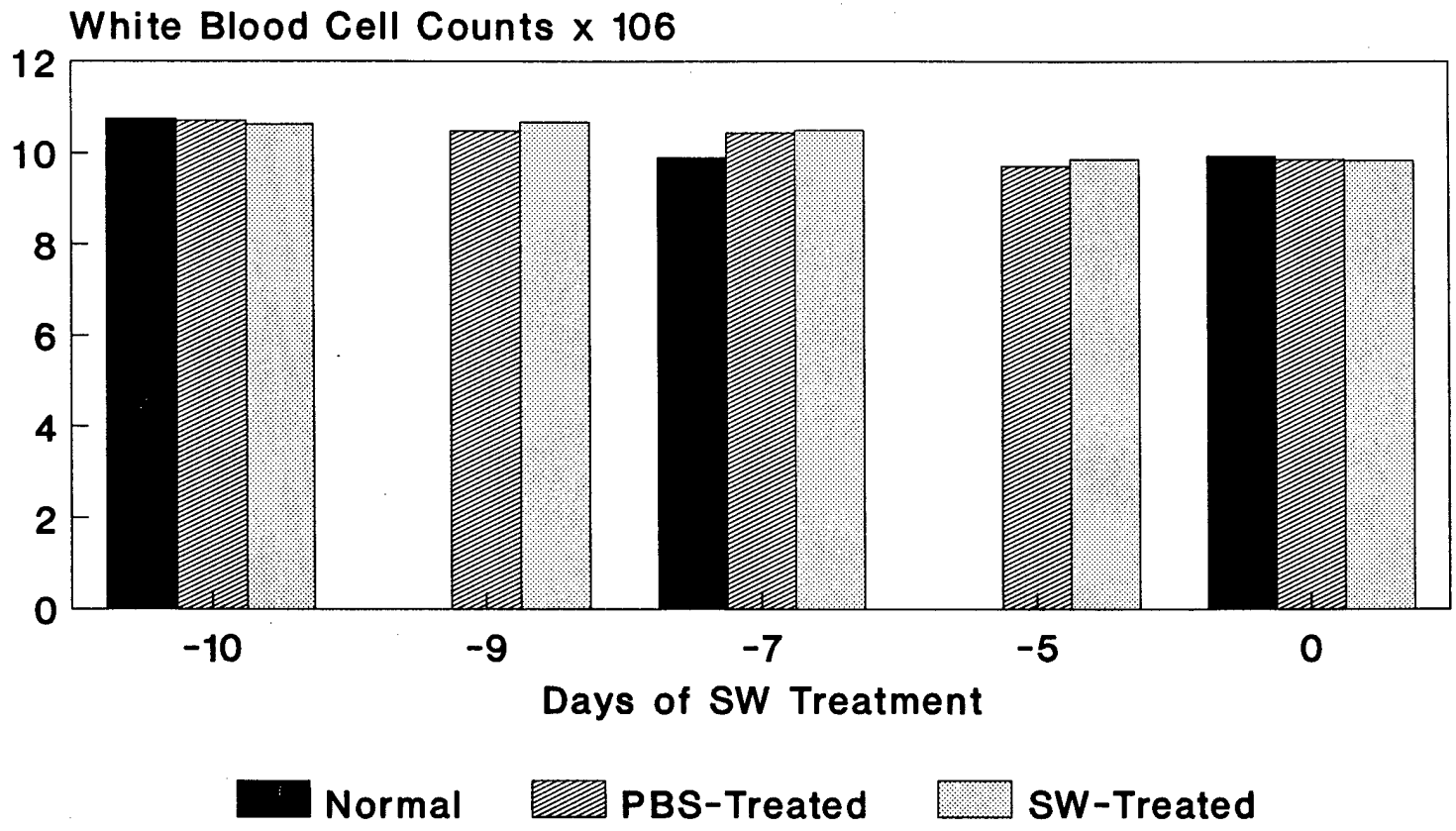

Figure 2b - White Blood Cell Counts During SW Treatment; WBCC = White Blood Cell Counts

Assessment of Duration of Effects of SW

Effects of SW on BM and Hematologic Parameters During SW Treatment

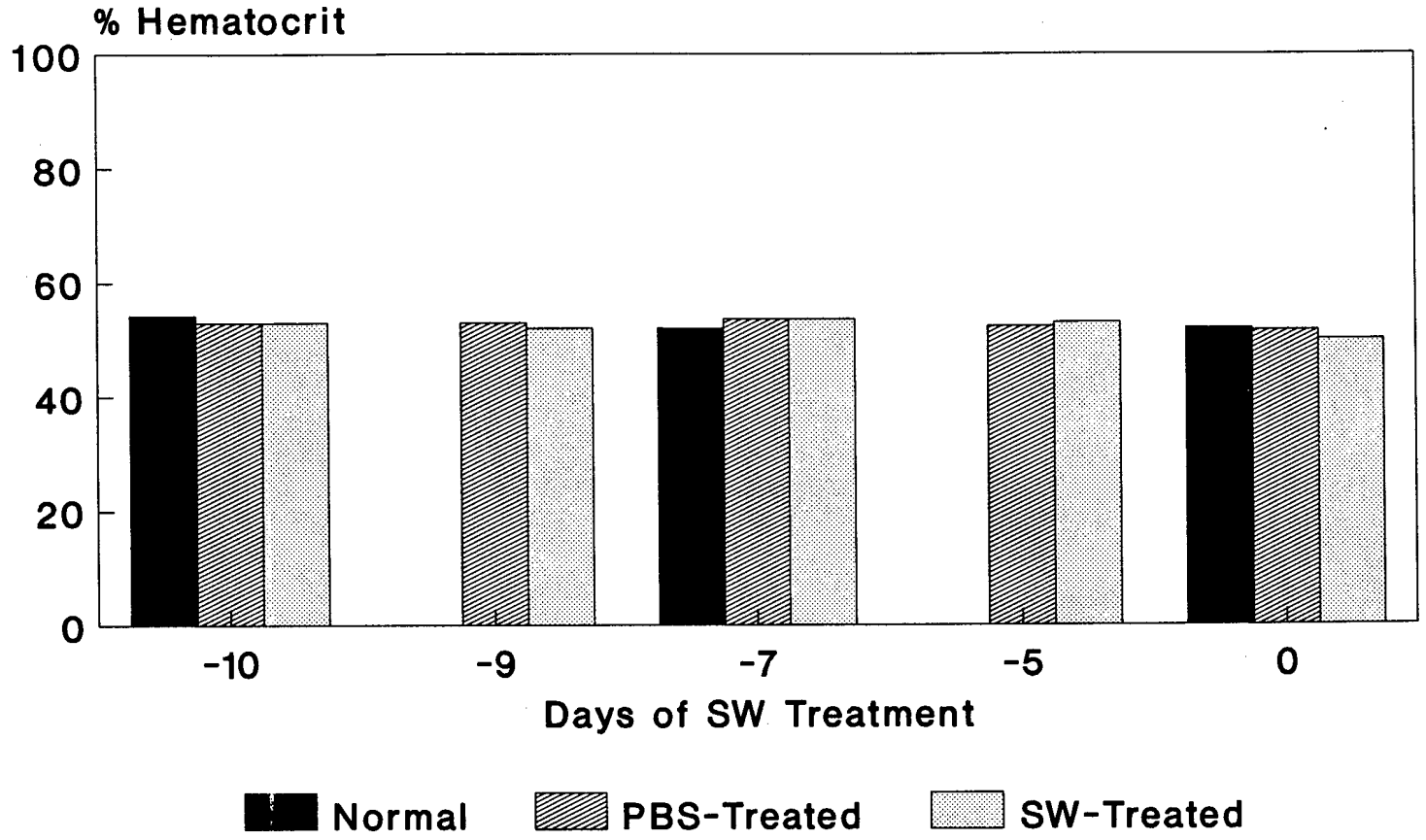

Figure 2c - % Hematocrit During SW Treatment

Assessment of Duration of Effects of SW

Effects of SW on Total Colony Forming Units During SW Treatment

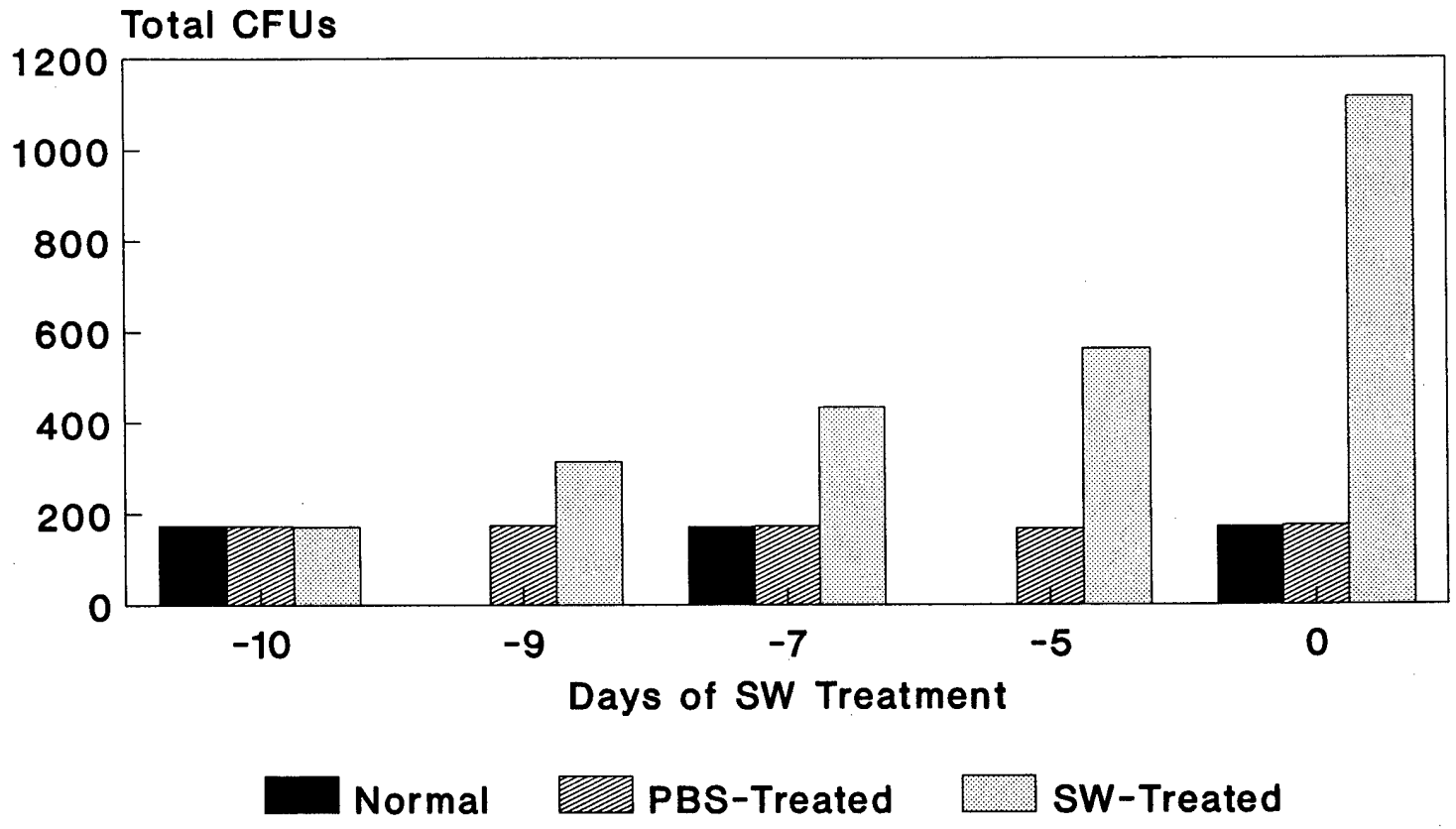

Figure 2d - Total Colony Forming Units During SW Treatment; CFU Total = Total Colony Forming Units

Assessment of Duration of Effects of SW

Effects of SW on Granulocyte-Macrophage Colony Forming Units During SW Treatment

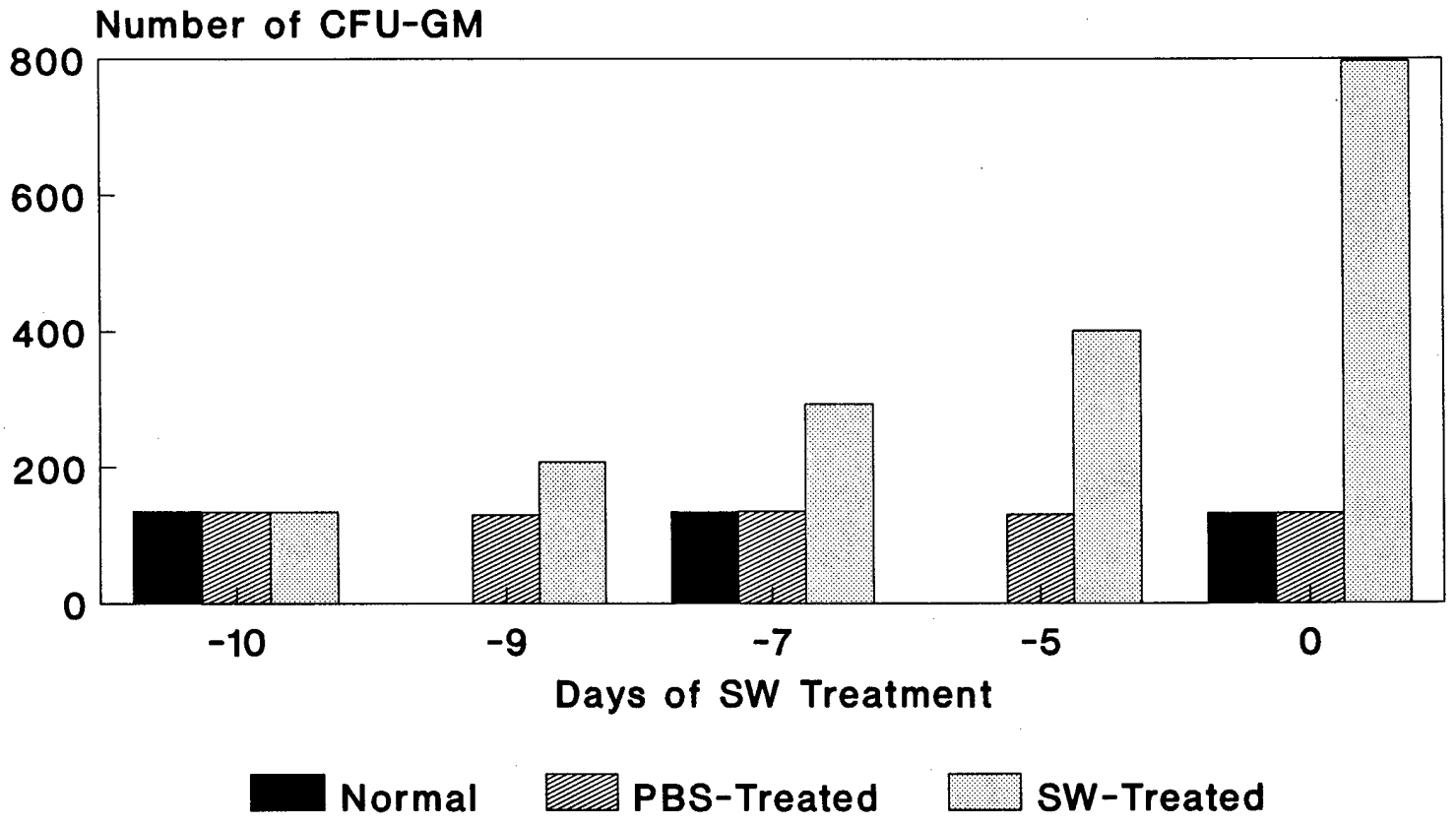

Figure 2e - CFU-granulocyte-macrophage During SW Treatment; CFU-GM = Granulocyte-Macrophage Colony Forming Units

Assessment of Duration of Effects of SW

Effects of SW on Burst Erythroid Colony Forming Units During SW Treatment

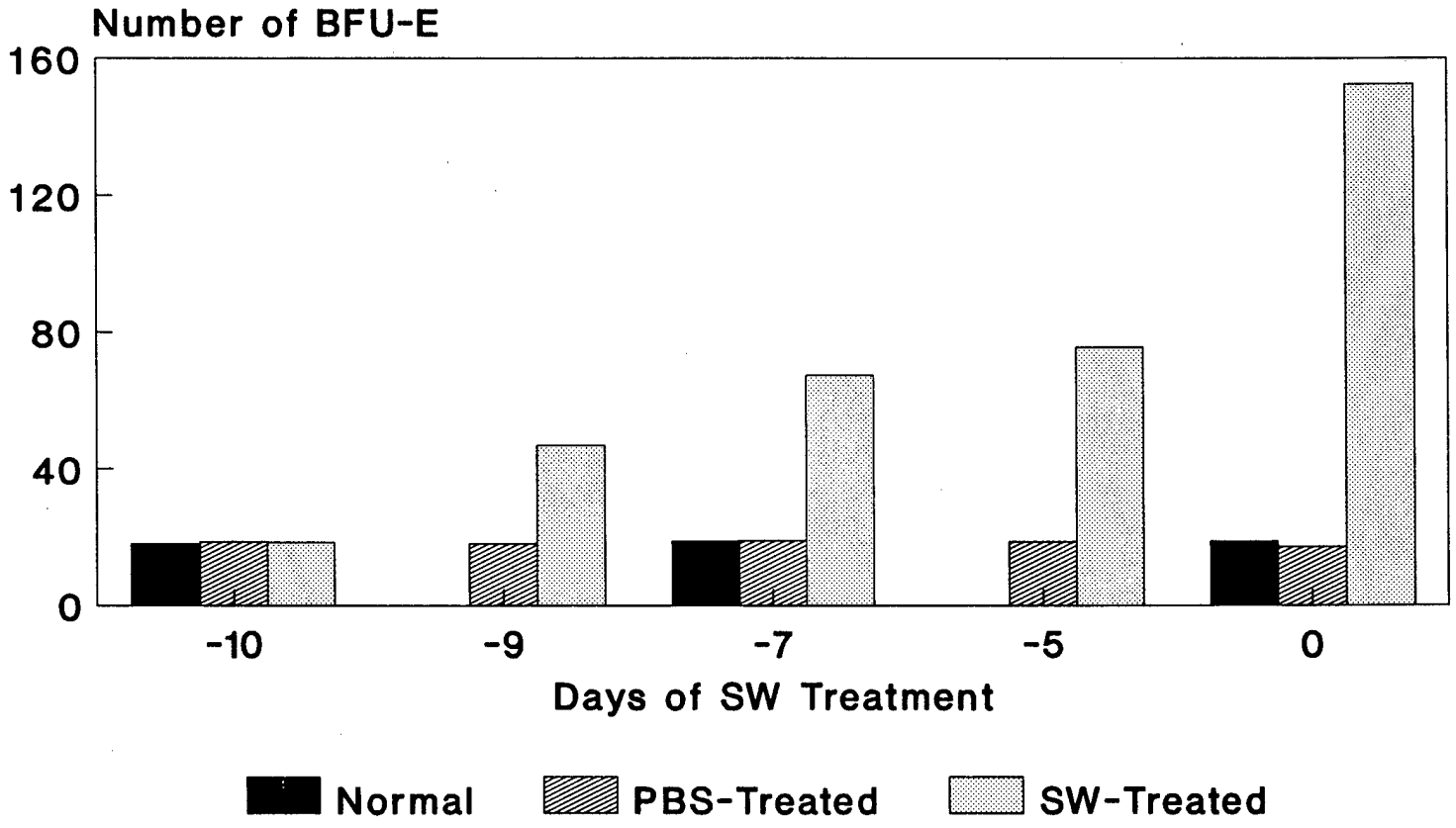

Figure 2f - Burst Erythroid During SW Treatment; BFU-E = Burst Erythroid Colony Forming Units

Assessment of Duration of Effects of SW

Effects of SW on GEMM

Colony Forming Units During SW Treatment

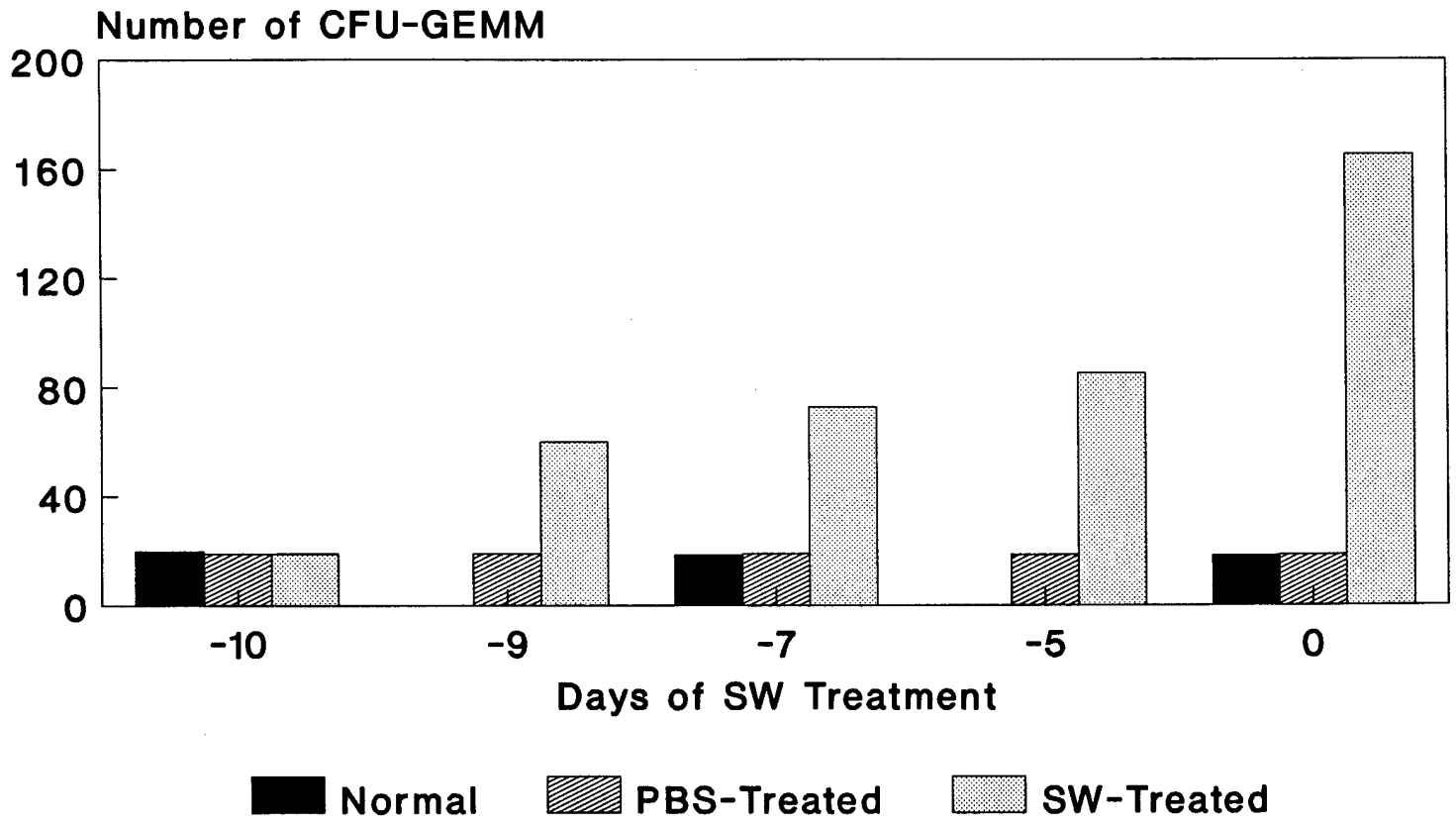

Figure 2g - Granulocyte-Erythroid-Macrophage- Colonies During SW Treatment; CFU-GEMM ▪ CFU-Mixed

Assessment of Duration of Effects of SW

BM Cellularity Following a Ten-day Treatment with SW

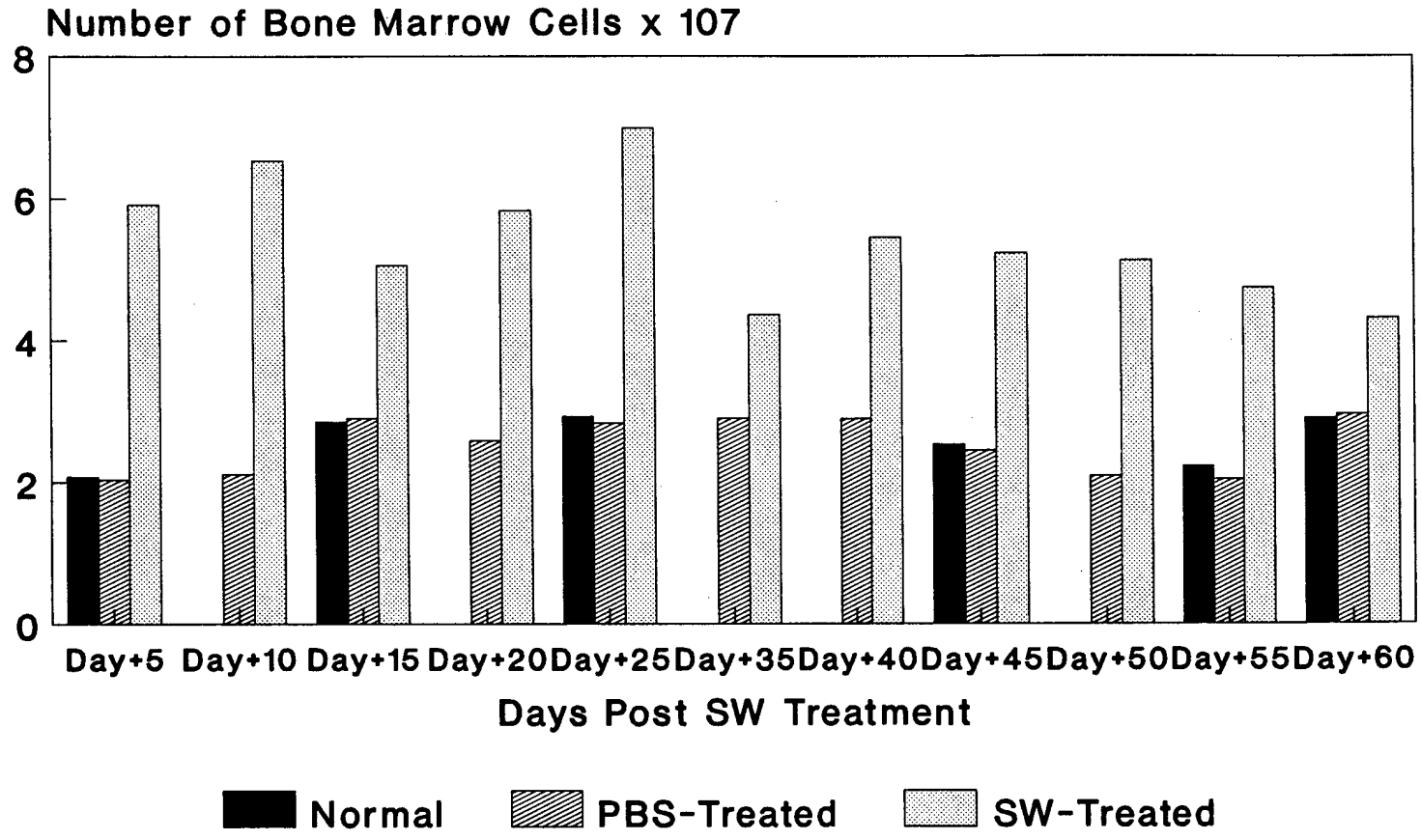

Figure 3a - BM Cellularity After SW Treatment; BM = Bone Marrow

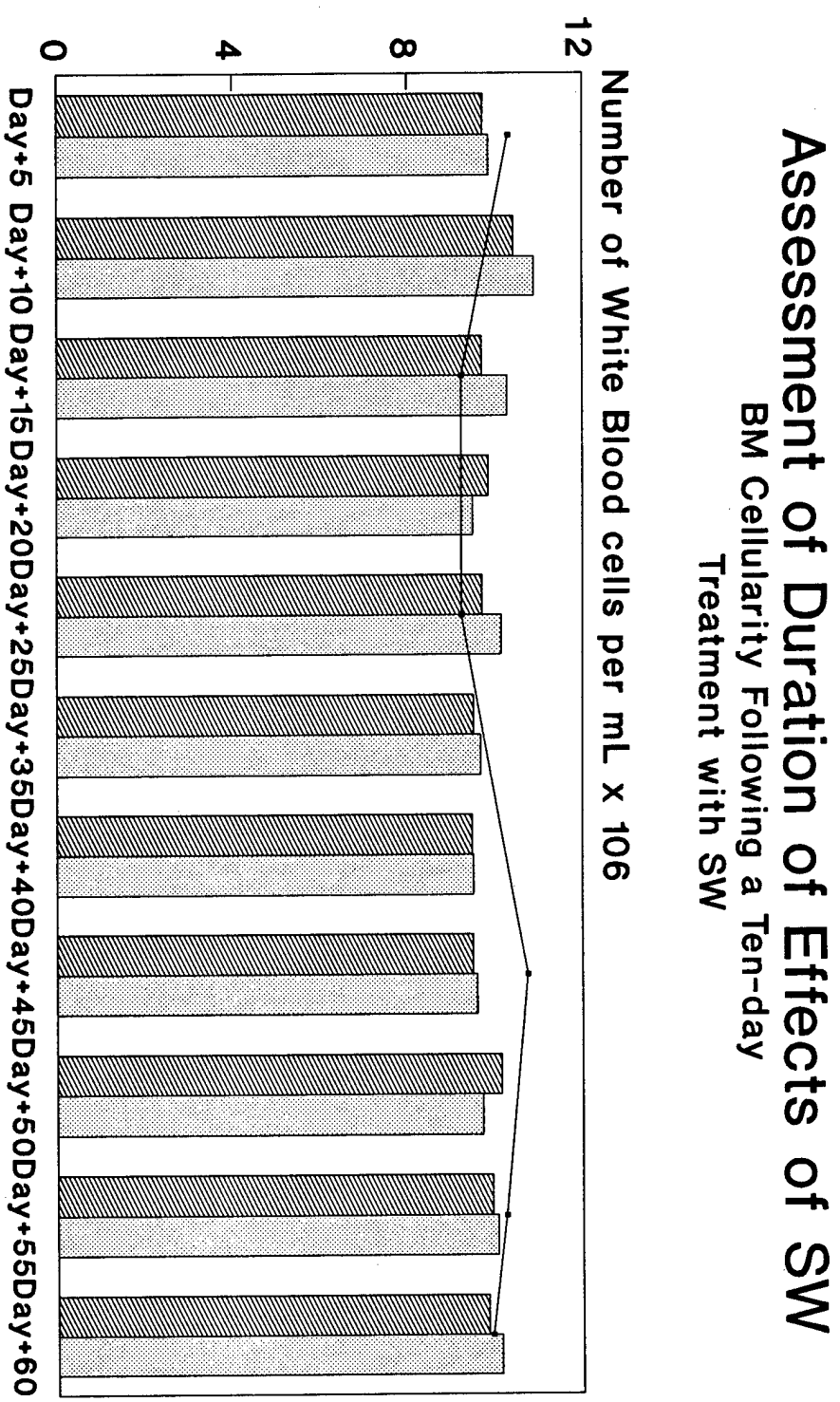

Figure 3b - White Blood Cell Counts After SW Treatment; WBCC = White Blood Cell Counts expressed as numbers/mL

Assessment of Duration of Effects of SW

Percent Hematocrit Following a Ten-day Treatment with SW

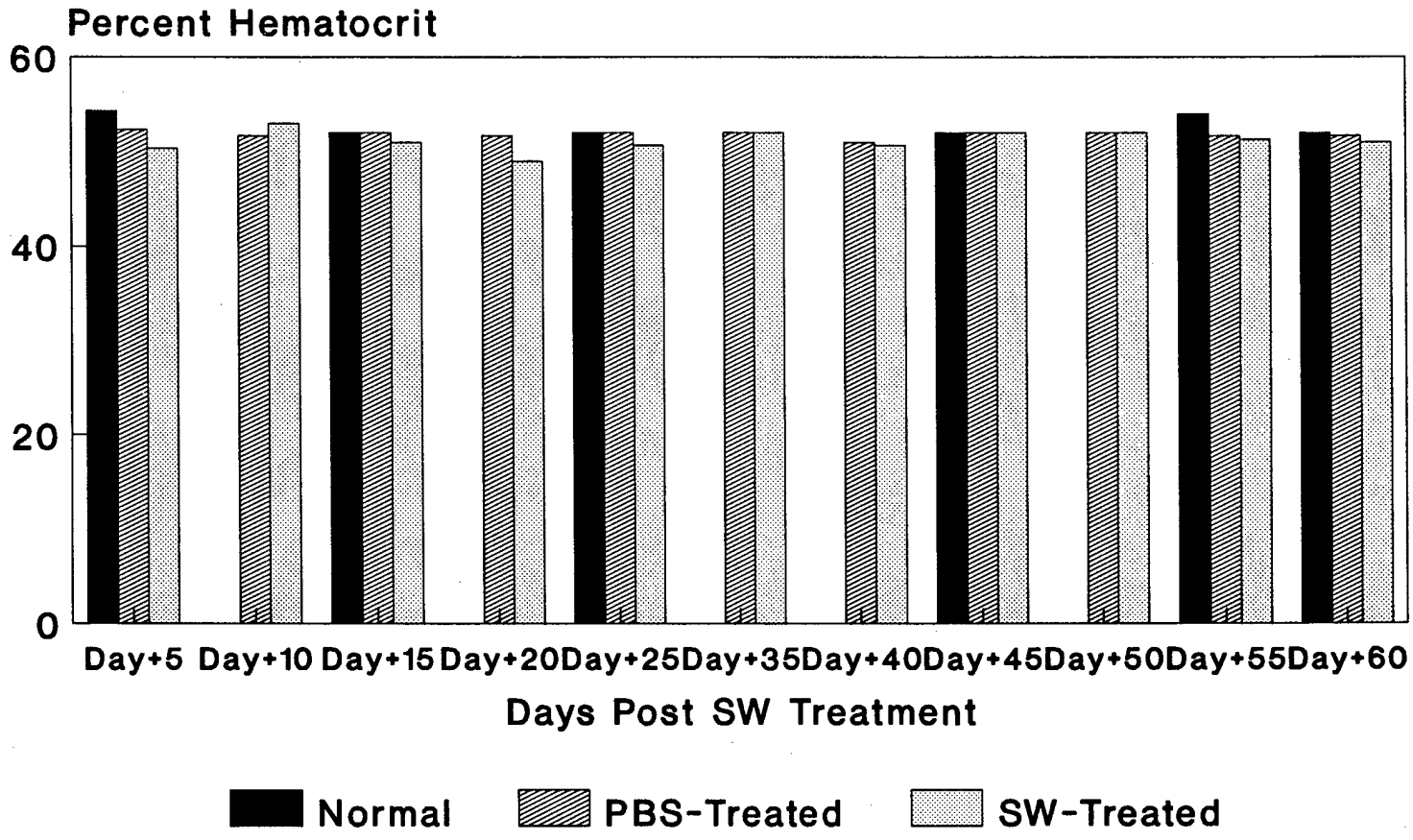

Figure 3c - Percent Blood Hematocrit After SW Treatment.

Assessment of Duration of Effects of SW

Effects on Total Colony Forming Units Following Treatment with SW

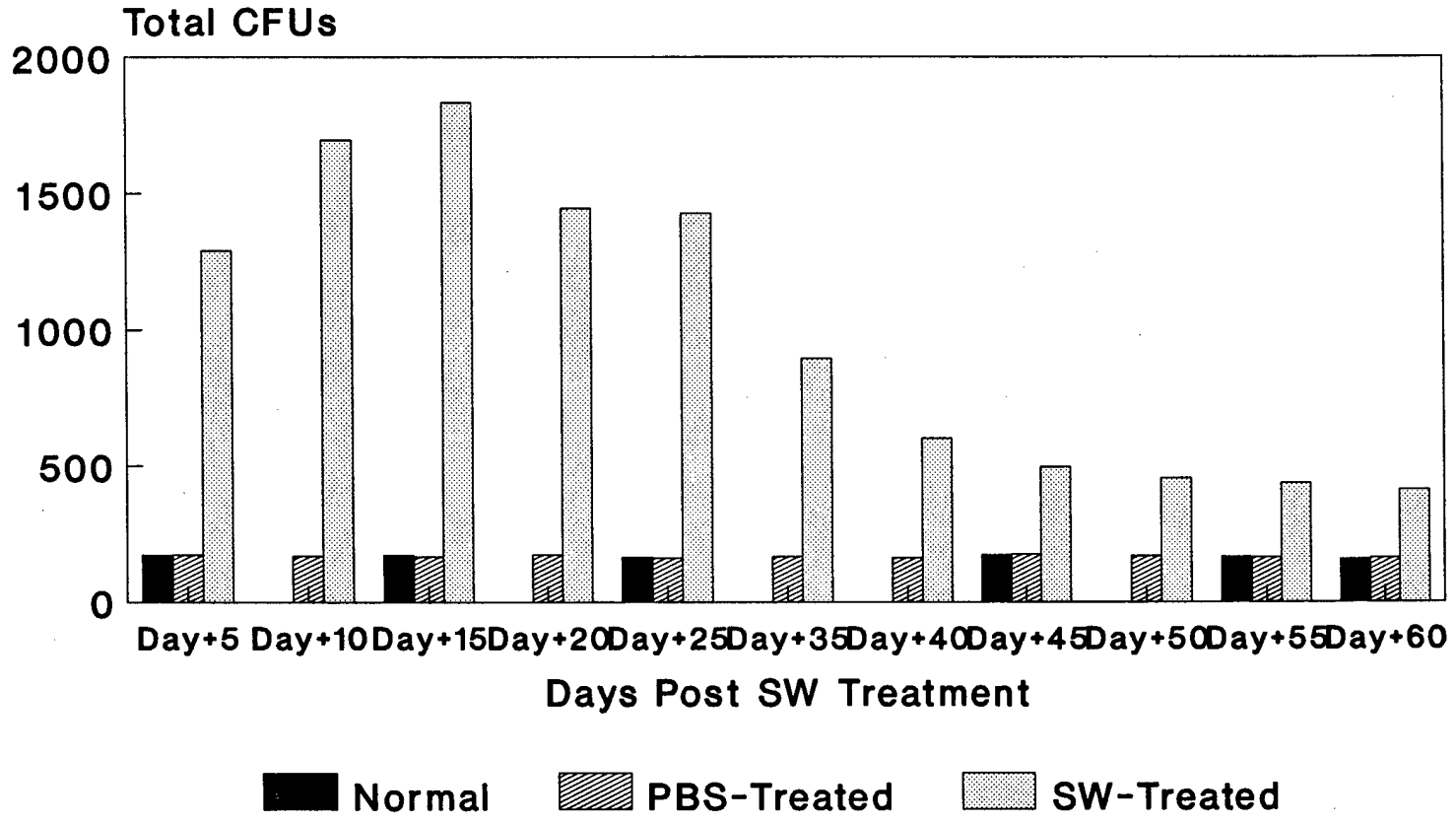

Figure 3d - Total Colony Forming Units After SW Treatment; CFU Total = Total Colony Forming Units

Assessment of Duration of Effects of SW

Effects on Granulocyte-Macrophage Colony Units Following Treatment with SW

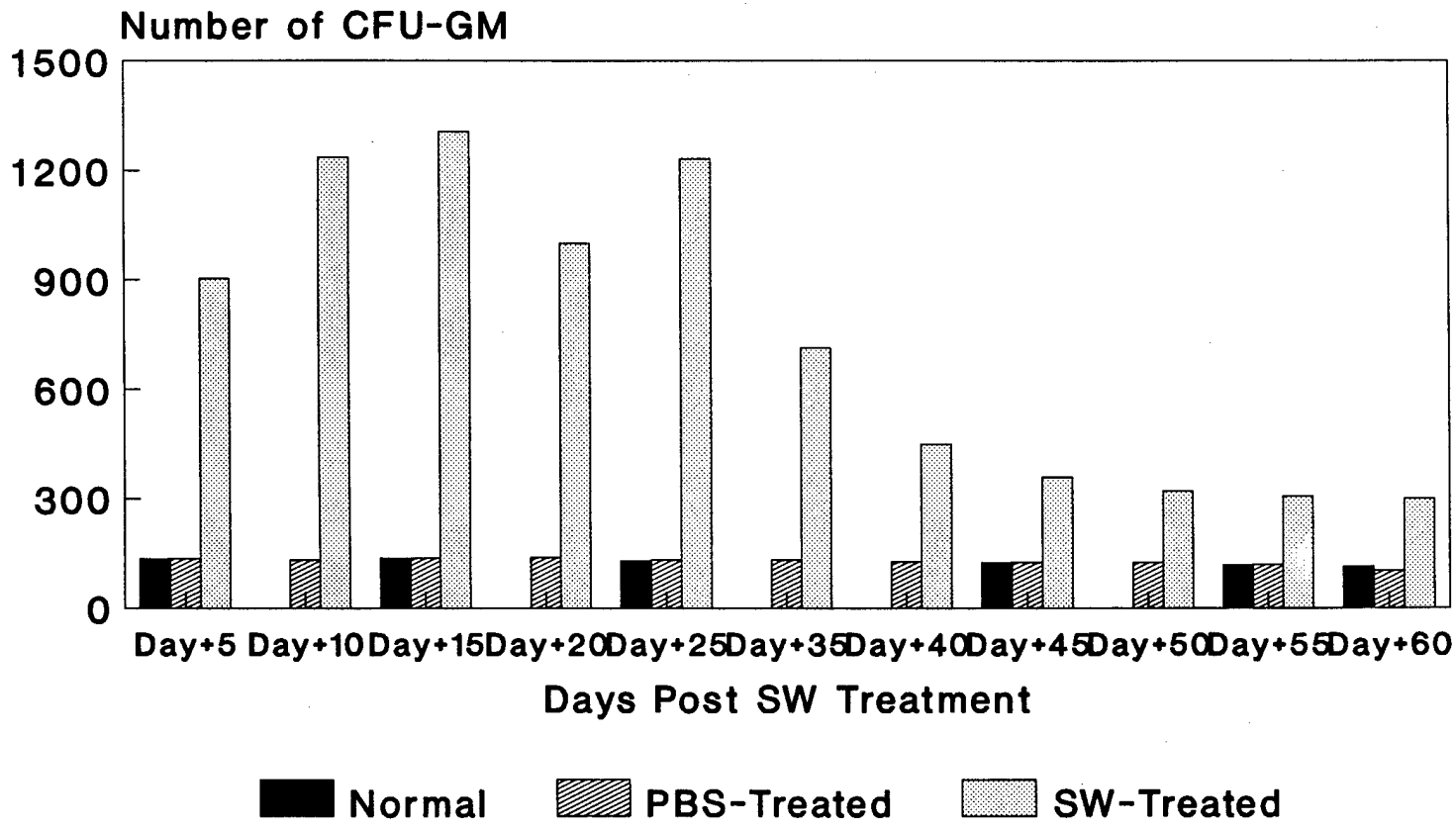

Figure 3e - CFU-granulocyte-macrophage After SW Treatment; CFU-GM = Granulocyte -Macrophage Colony Forming Units

Assessment of Duration of Effects of SW

Effects on Burst Erythroid Colony Units Following Treatment with SW

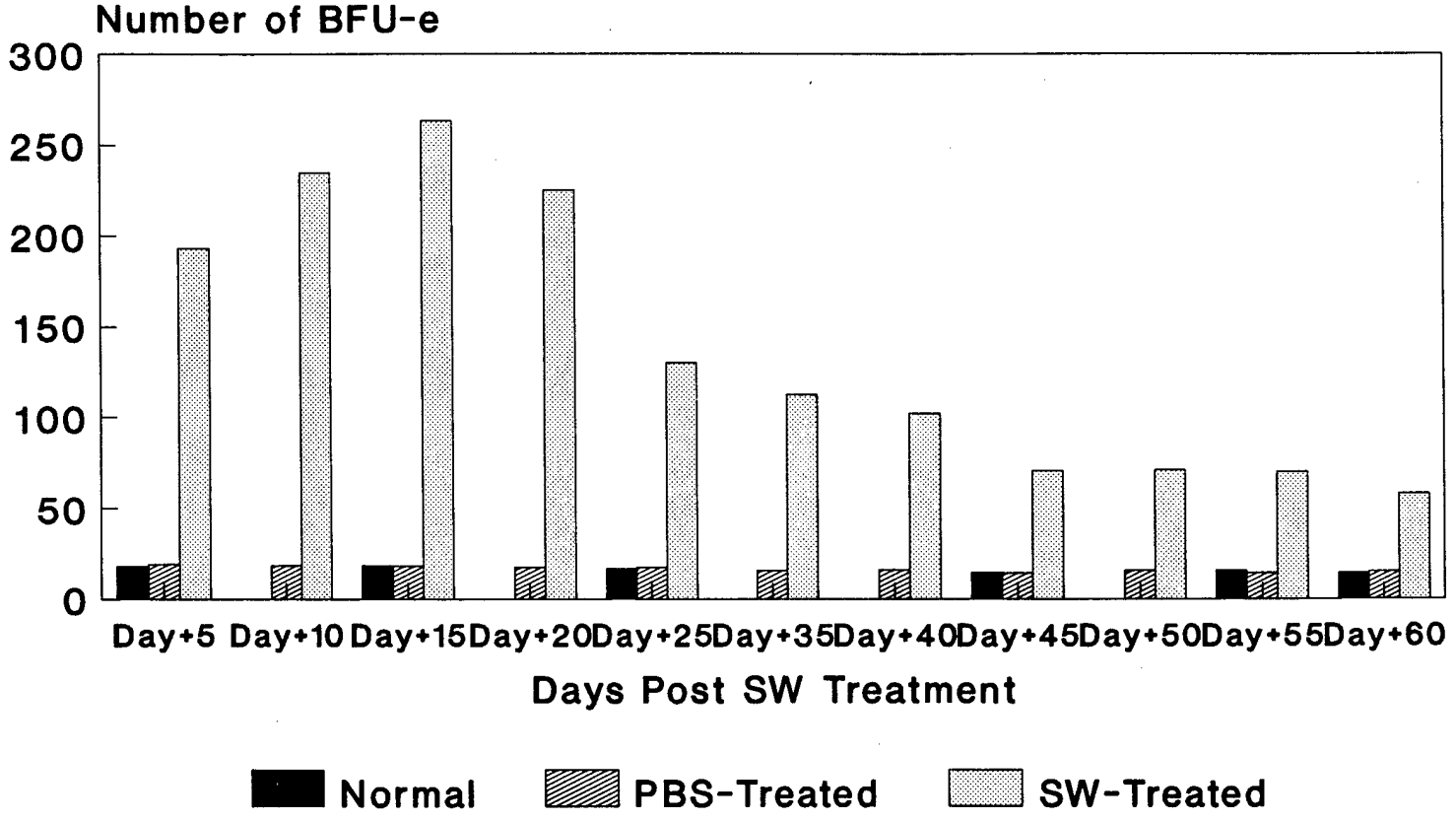

Figure 3f - Burst Erythroid After SW Treatment; BFU-E = Burst Erythroid Colony Forming Units

Assessment of Duration of Effects of SW

Effects on GEMM Colony Units Following Treatment with SW

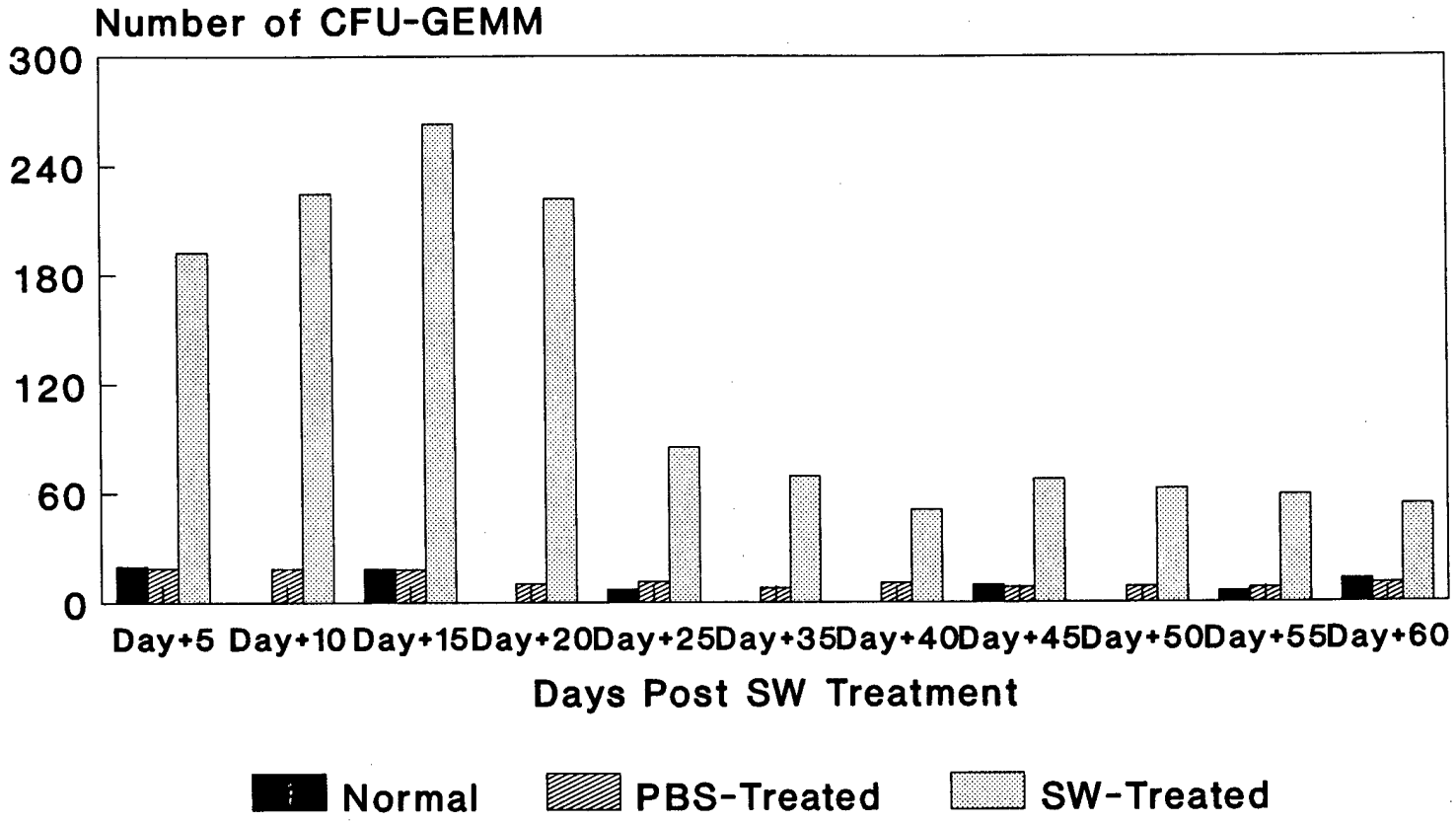

Figure 3g - Granulocyte-Erythroid-Macrophage- Colony Forming Units After SW Treatment; CFU-GEMM ▪ CFU-Mixed

Survival of Mice During Chemotherapy

Effects of SW on Survival of Mice During Intensive High-Dose Chemotherapy

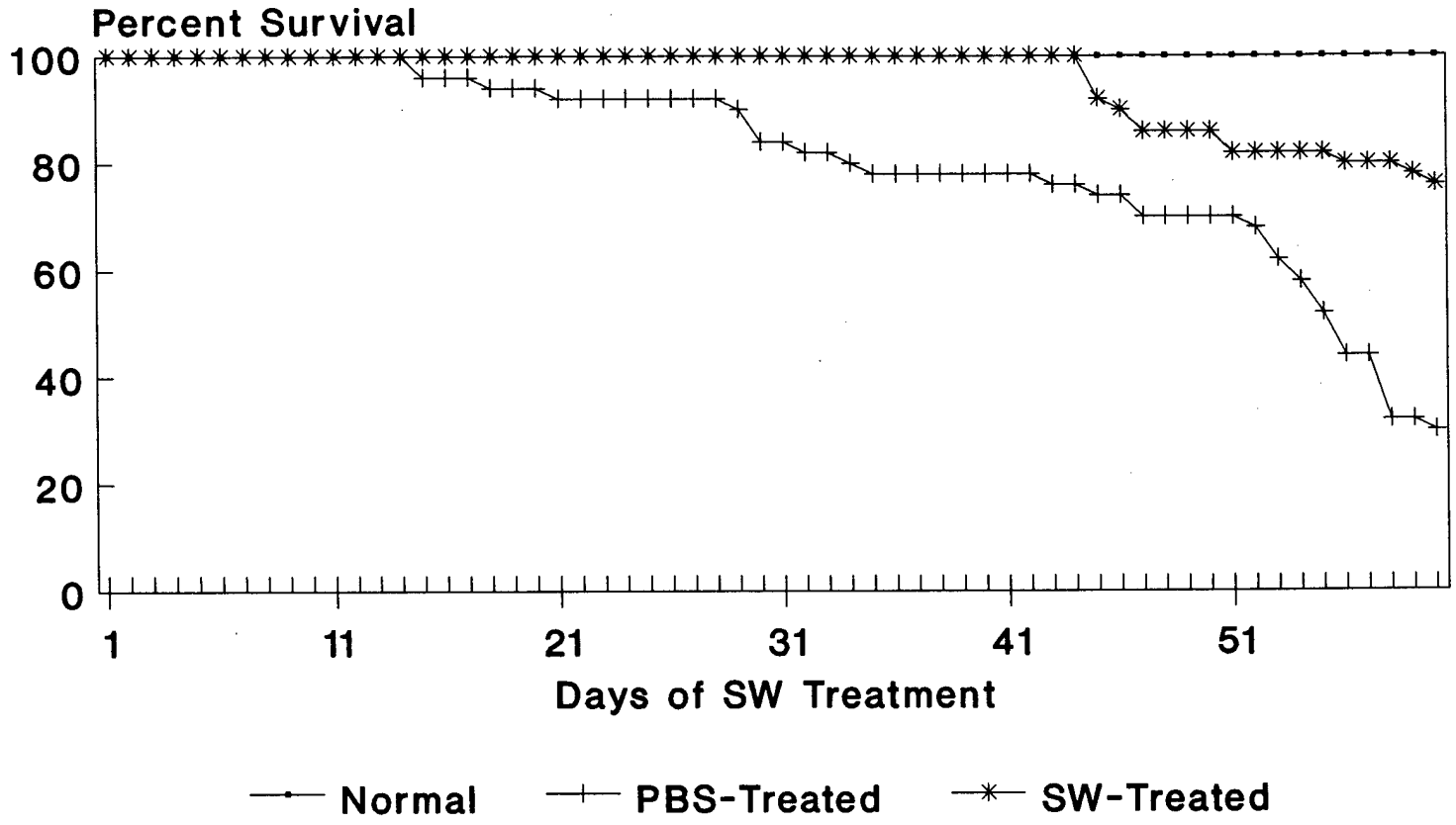

Figure 4-1st SW/PBS PreRx-Days 1-10; LD10 DOX was injected on Days 11, 26 & 40; 2nd SW/PBS Rx-Days 55-64; LD10 DOX o

Survival of Mice During Chemotherapy

Effects of SW on Survival of Mice During Intensive High-Dose Chemotherapy

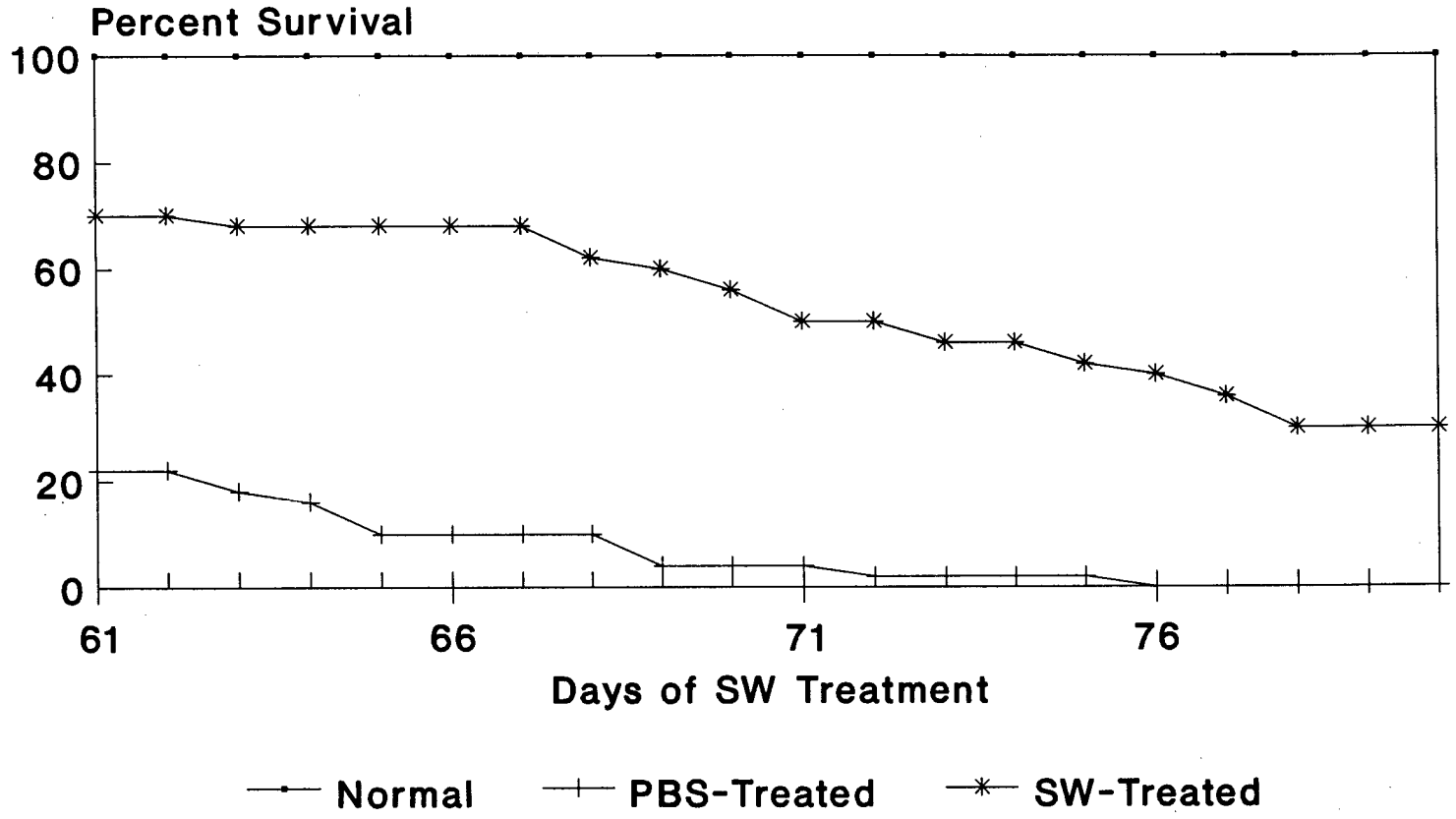

Figure 4-Contd. 2nd SW/PBS Rx-Days 55-64
LD10 DOX was injected on Days 11, 26, 40 and 65.

Survival of Mice During Chemotherapy

Effects of SW on Bone Marrow Cellularity During Intensive & High-Dose Chemotherap

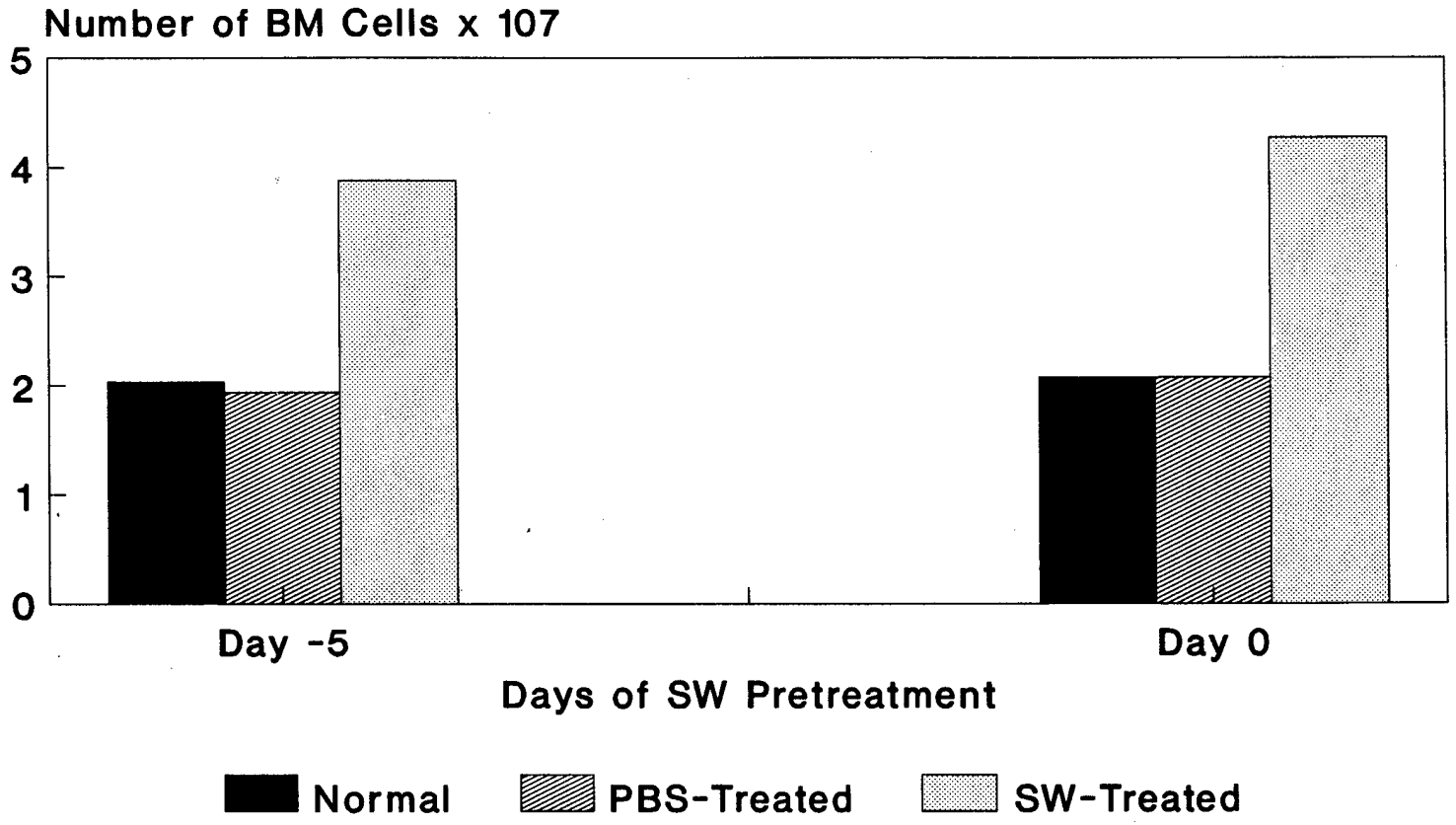

Figure 4A - Effects of SW Pretreatment on Bone Marrow Cellularity;
BM = Bone Marrow

Survival of Mice During Chemotherapy

Effects of SW on Bone Marrow Cellularity During Intensive & High-Dose Chemotherap

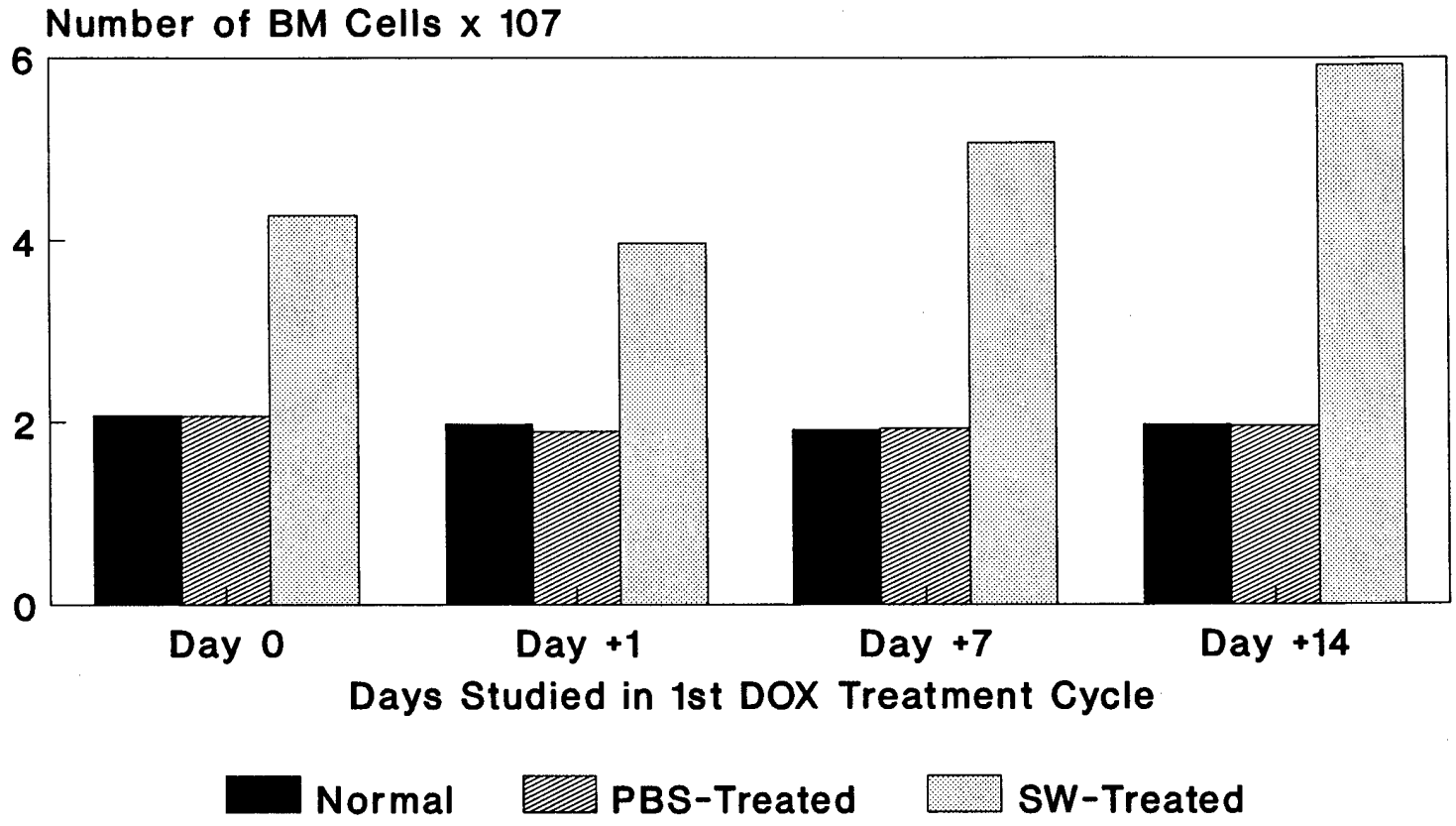

Figure 4B - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on Bone Marrow Cellularity During Intensive & High-Dose Chemotherap

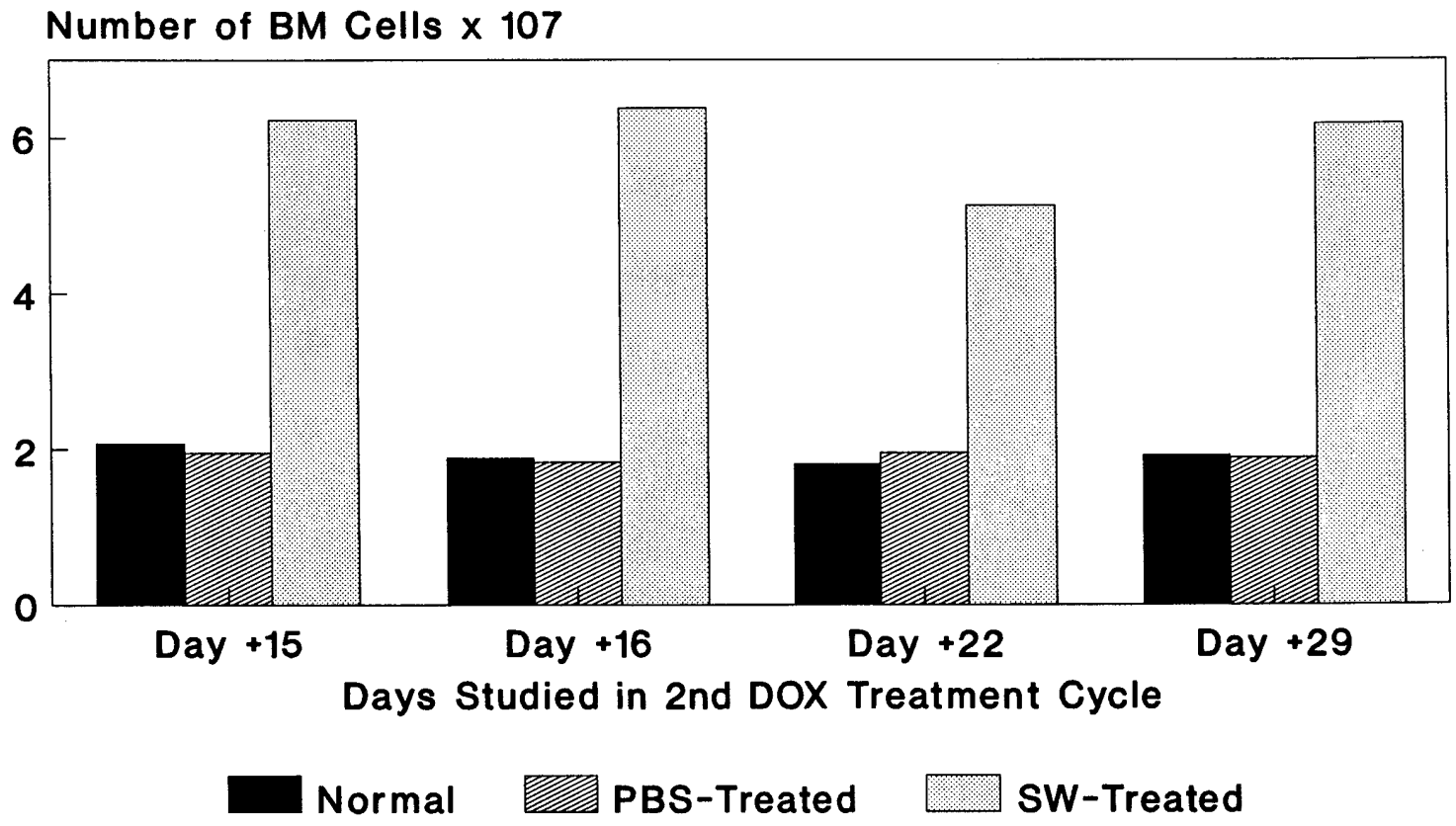

Figure 4C - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on Bone Marrow Cellularity During Intensive & High-Dose Chemotherap

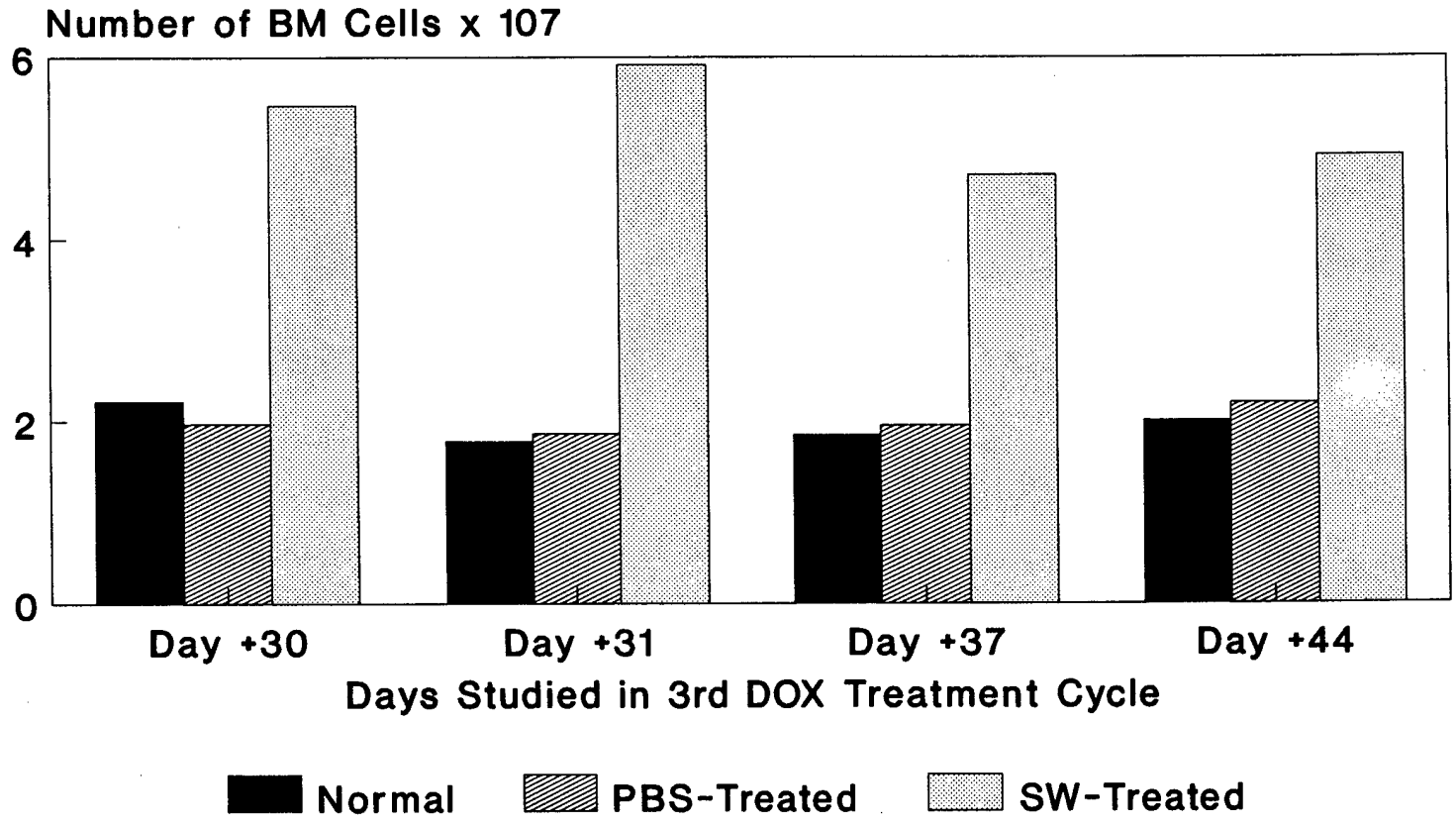

Figure 4D - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on Bone Marrow Cellularity During Intensive & High-Dose Chemotherap

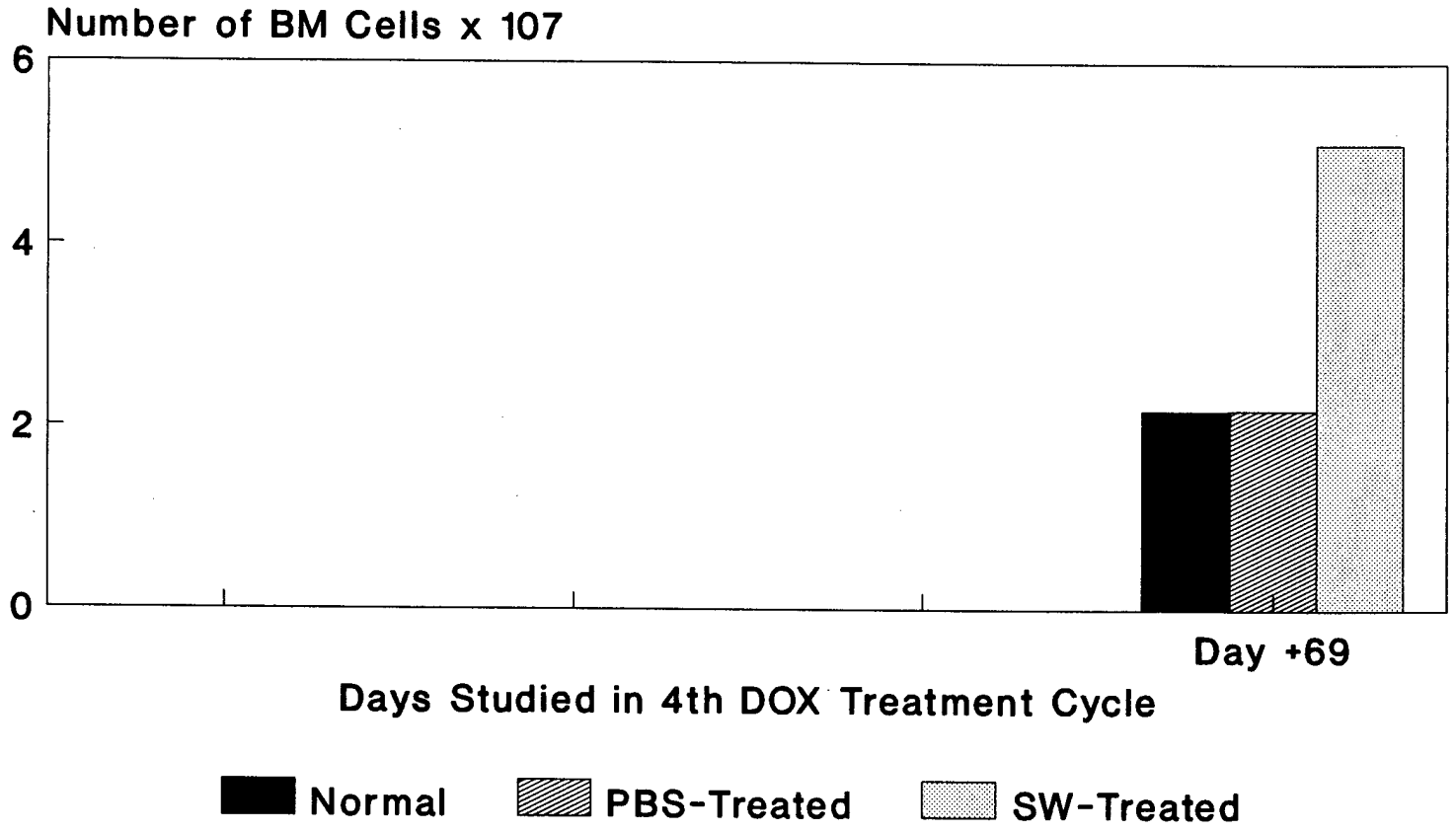

Figure 4E - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on White Blood Cell Counts During Intensive High-Dose Chemotherapy

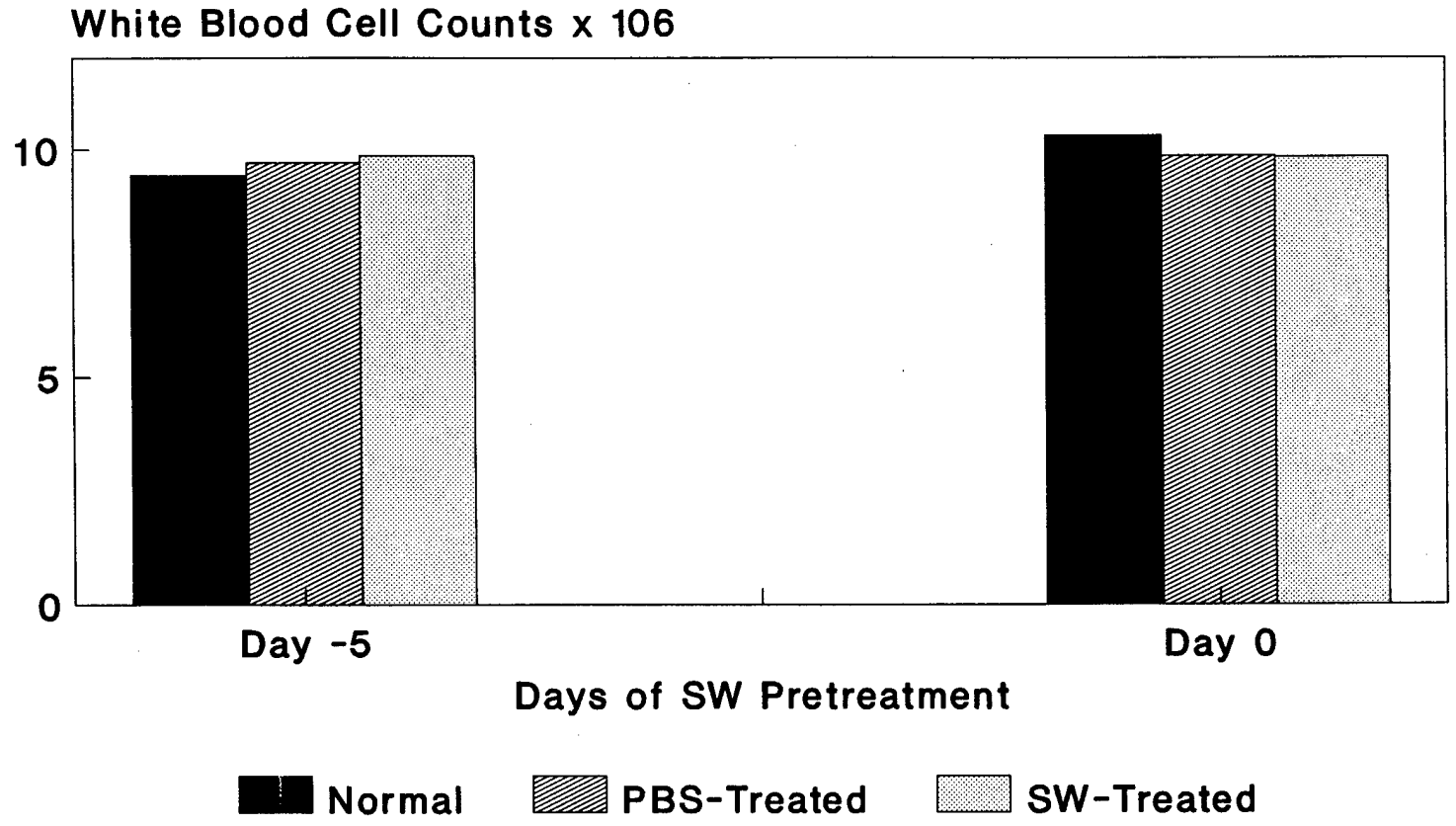

Figure 4F - Effects of SW Pretreatment on White Blood Cell Counts; WBCC = White Blood Cell Counts

Survival of Mice During Chemotherapy

Effects of SW on White Blood Cell Counts During Intensive High-Dose Chemotherapy

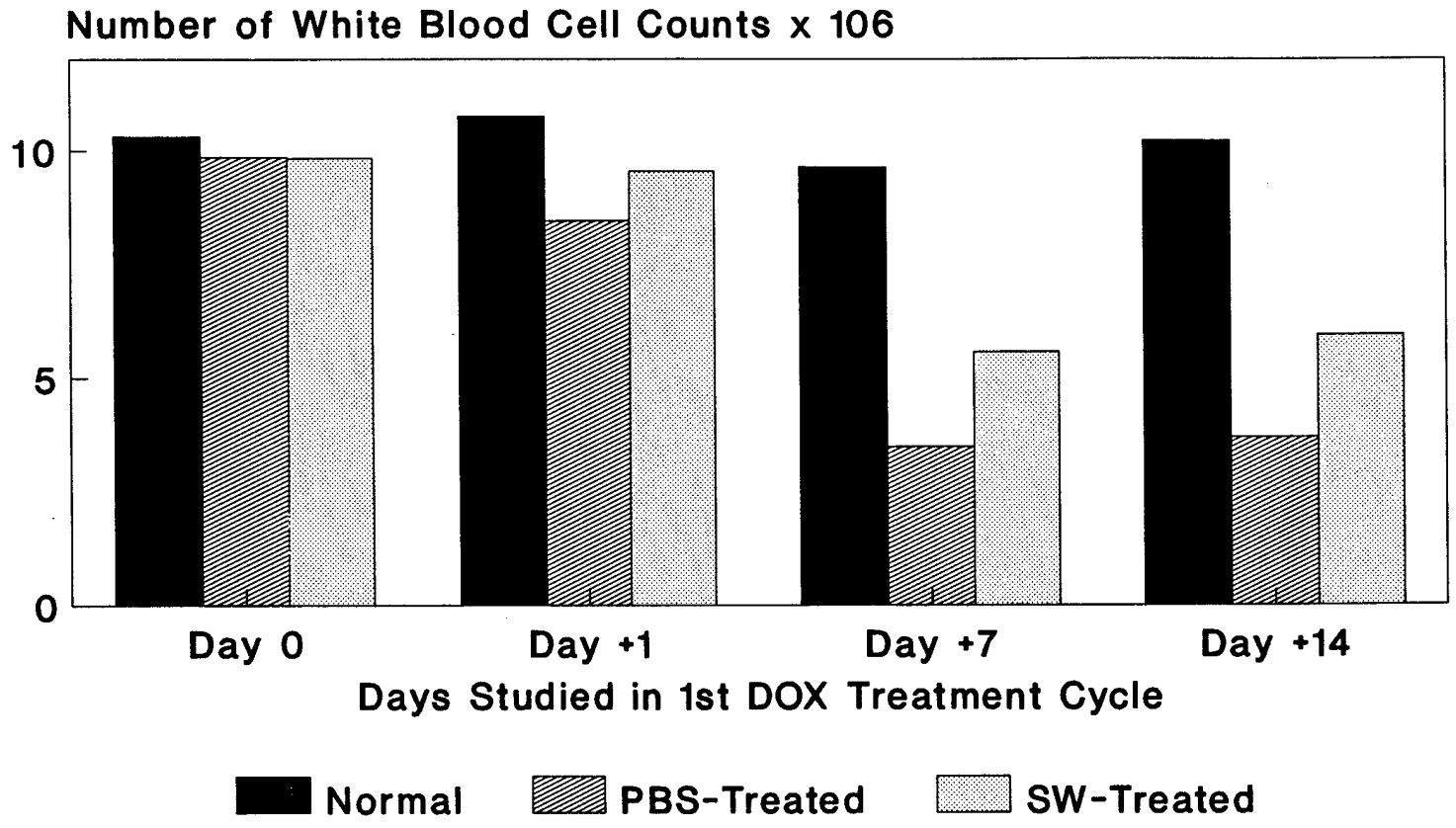

Figure 4G - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

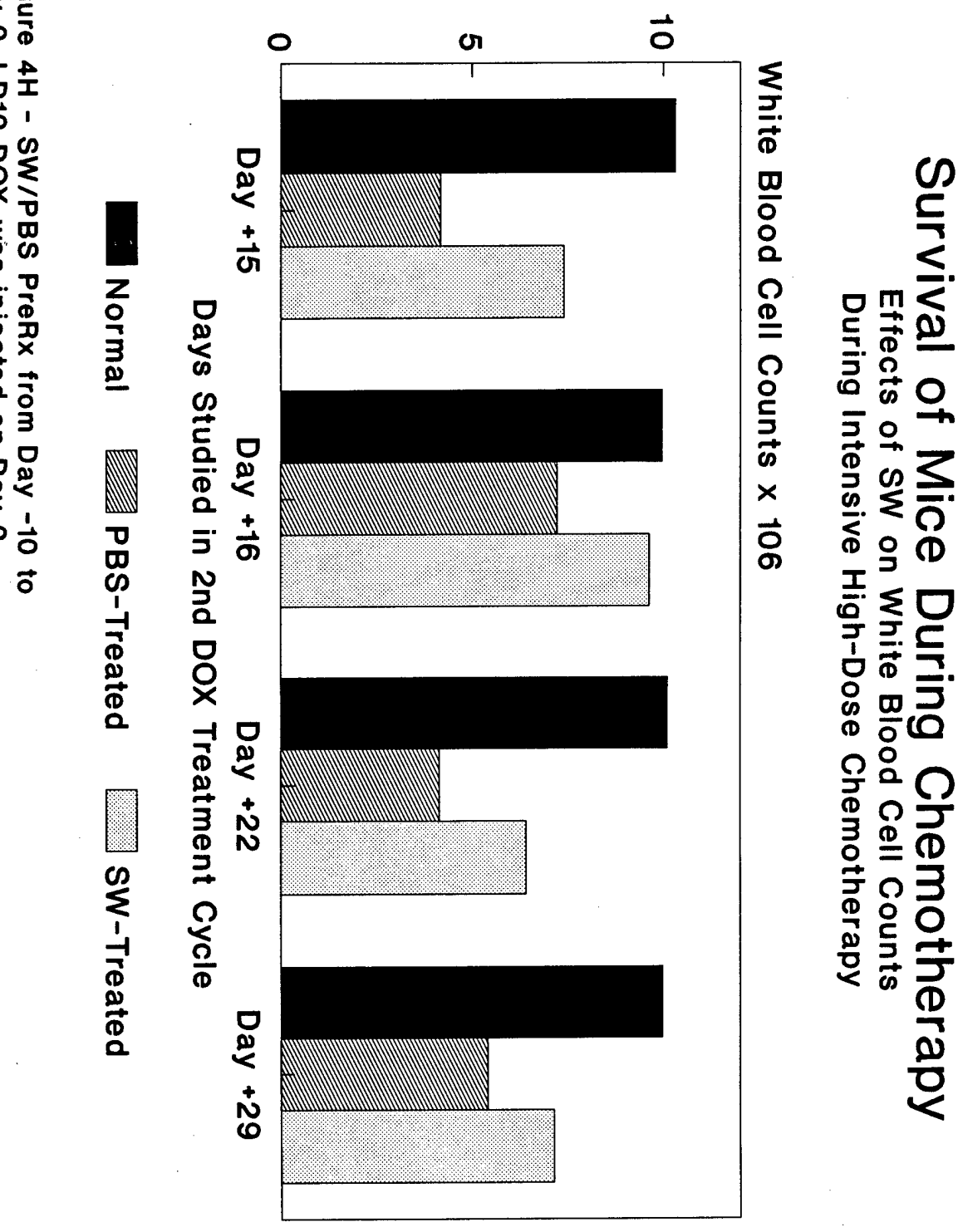

Figure 4H - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on White Blood Cell Counts During Intensive High-Dose Chemotherapy

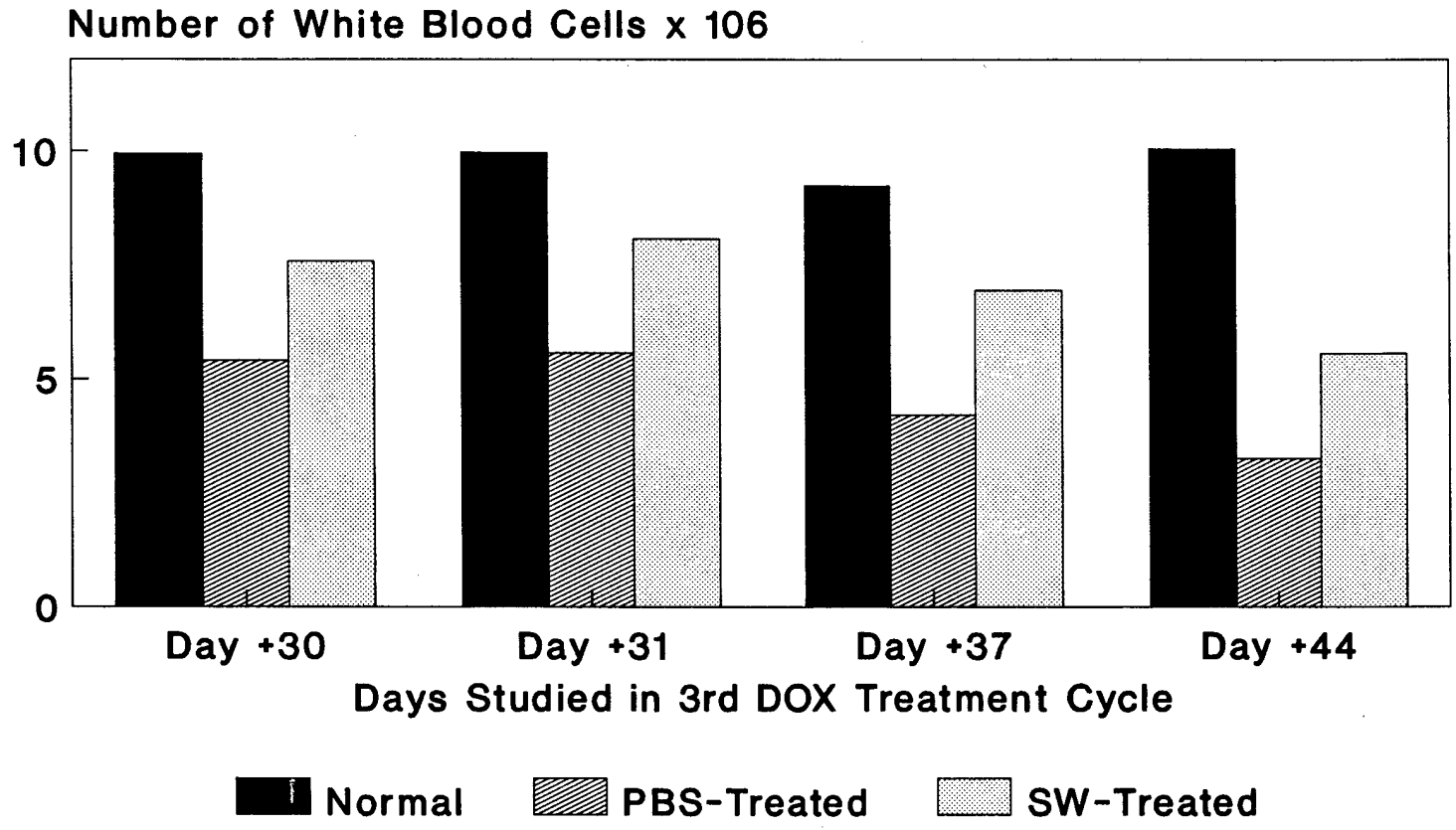

Figure 4I - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on White Blood Cell Counts During Intensive High-Dose Chemotherapy

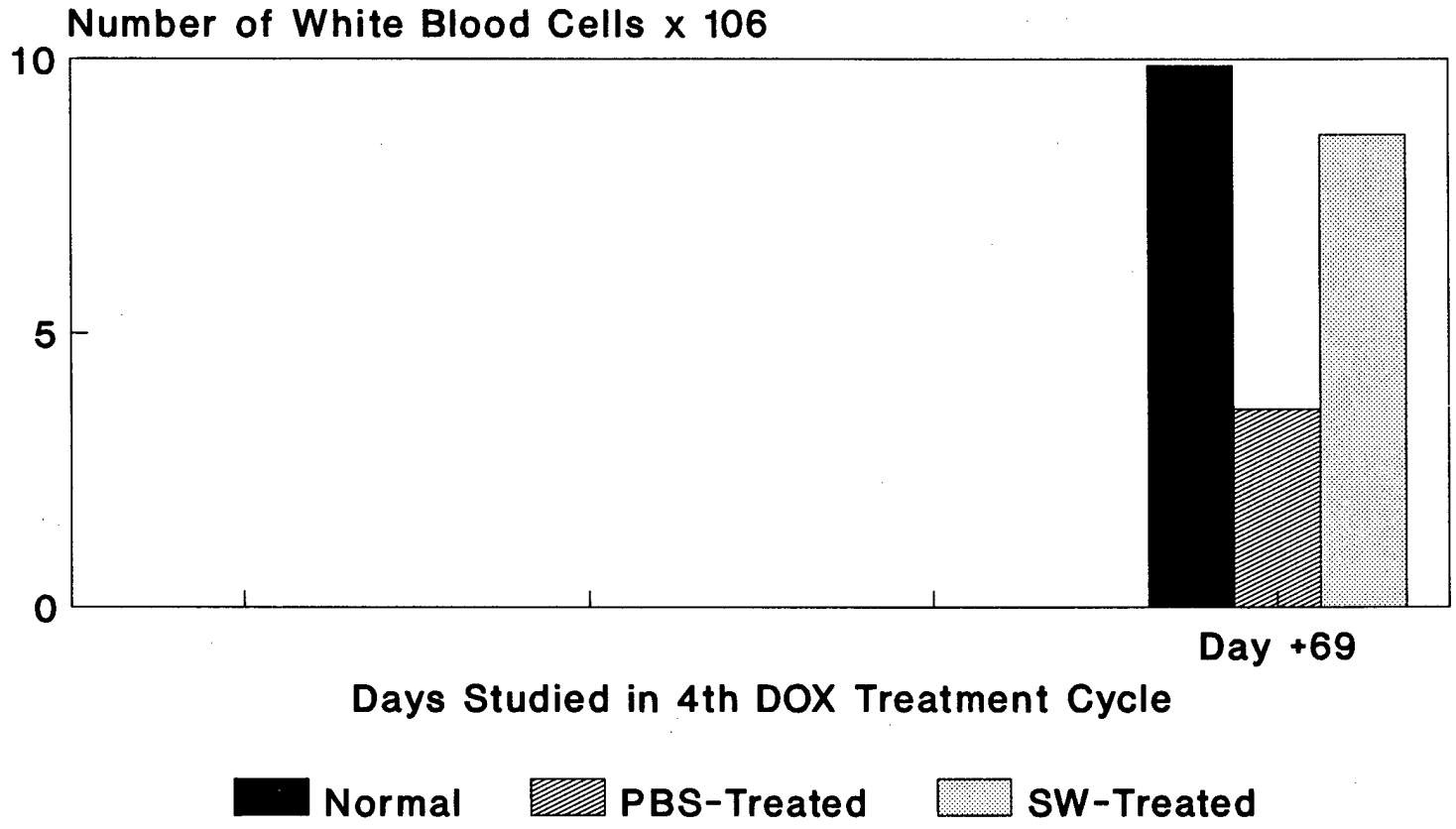

Figure 4J - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

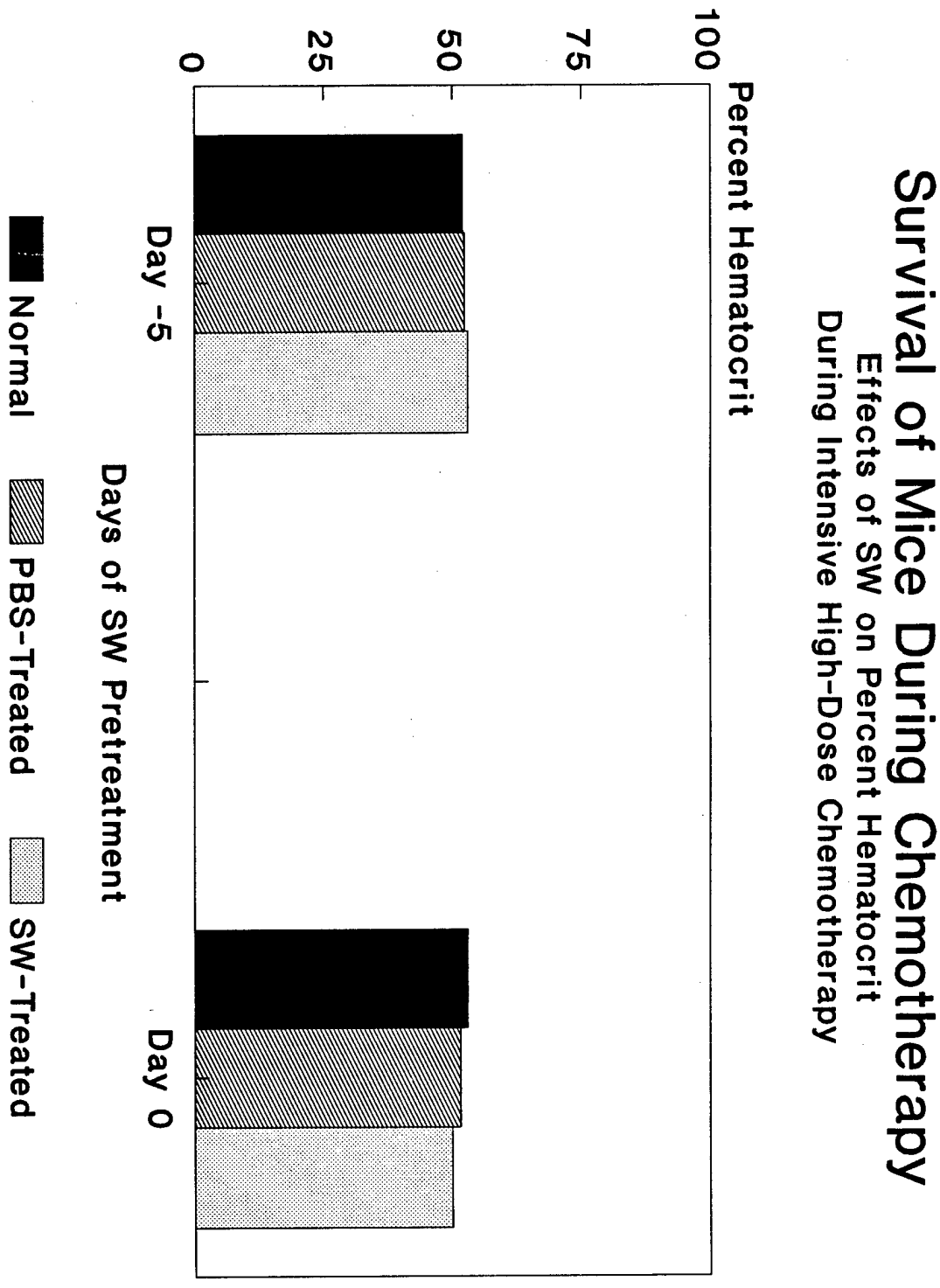

Figure 4K - Effects of SW Pretreatment on Percent Hematocrit;

Survival of Mice During Chemotherapy

Effects of SW on Percent Hematocrit During Intensive High-Dose Chemotherapy

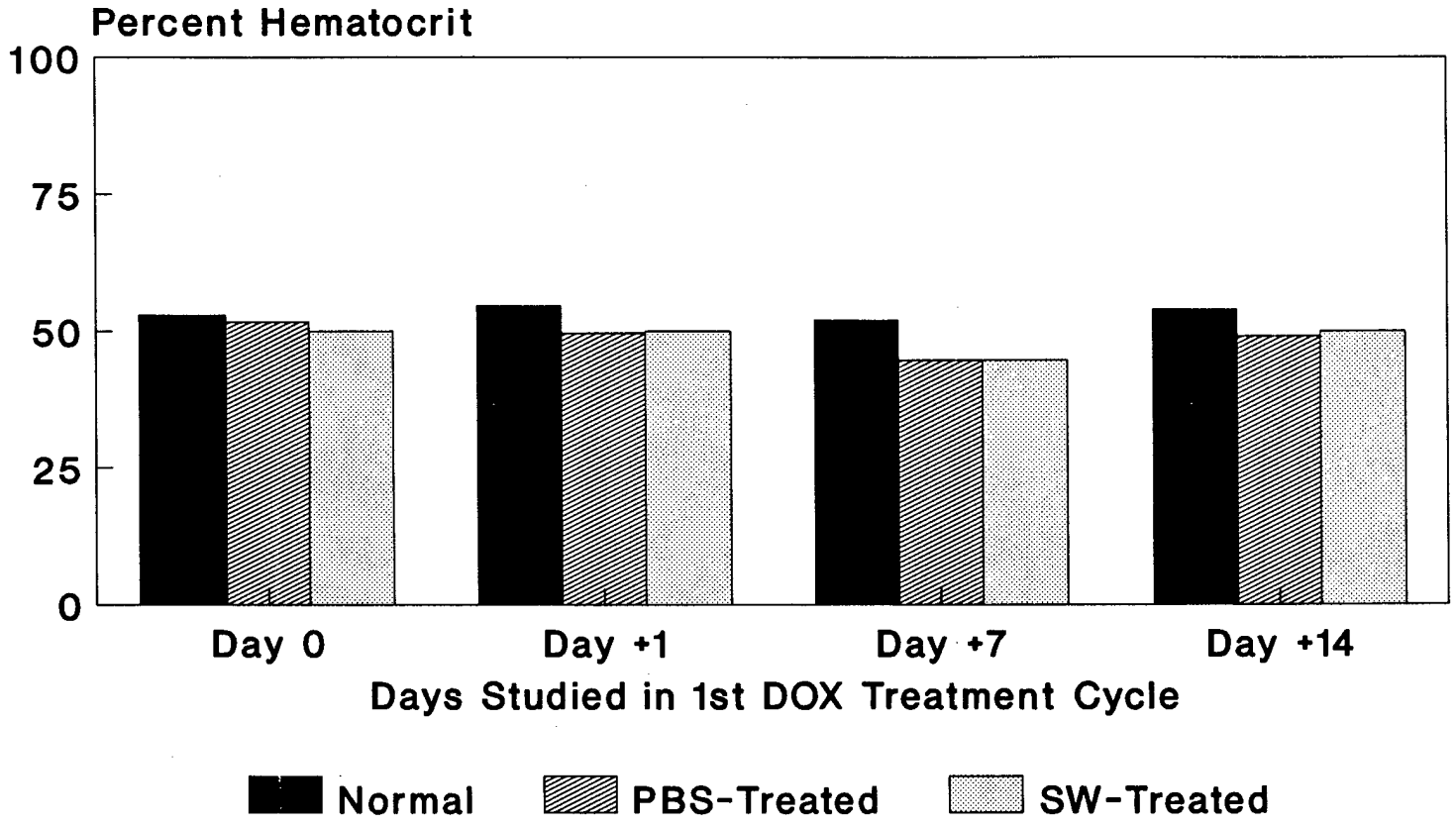

Figure 4L - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on Percent Hematocrit During Intensive High-Dose Chemotherapy

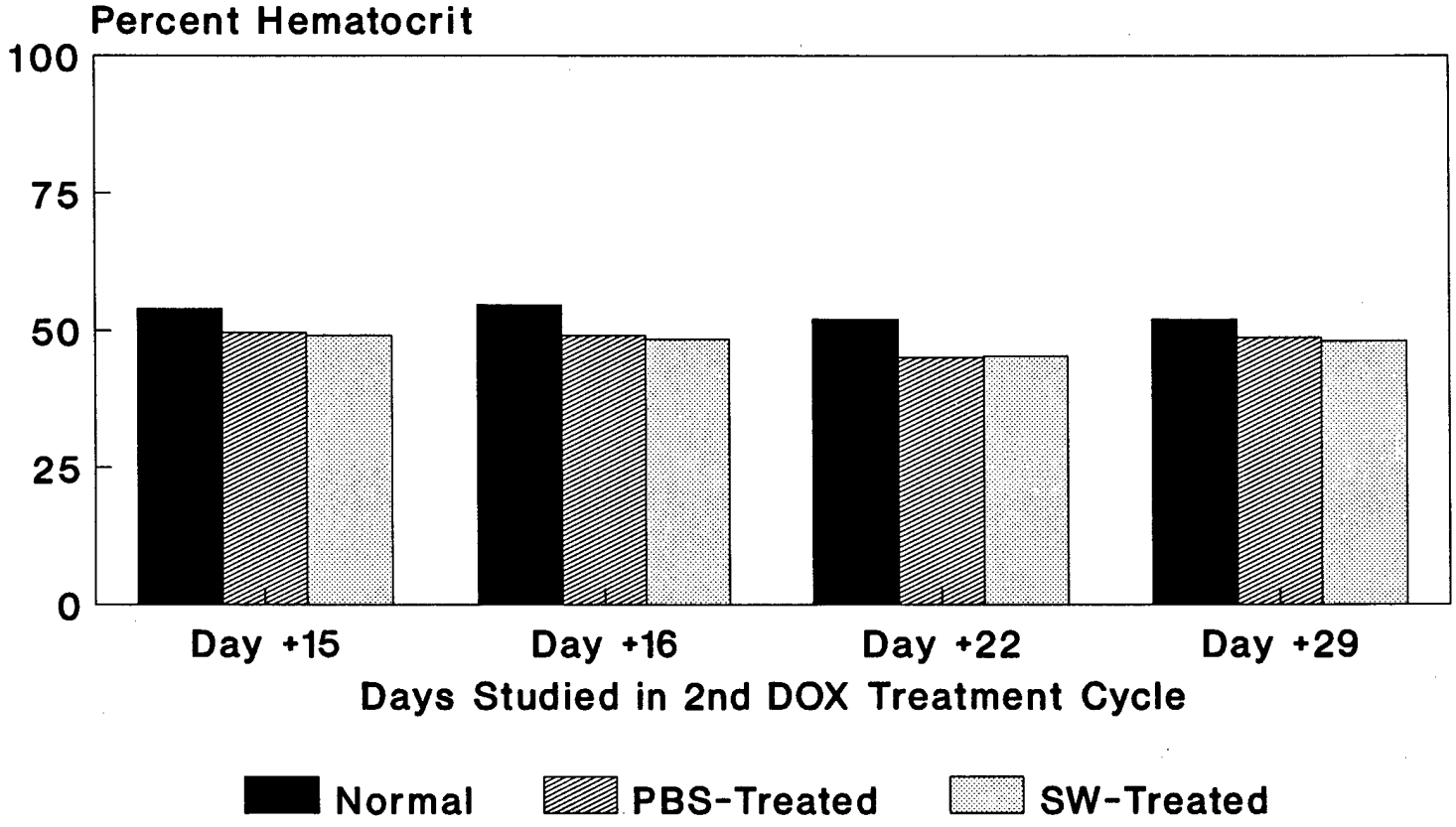

Figure 4M - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on Percent Hematocrit During Intensive High-Dose Chemotherapy

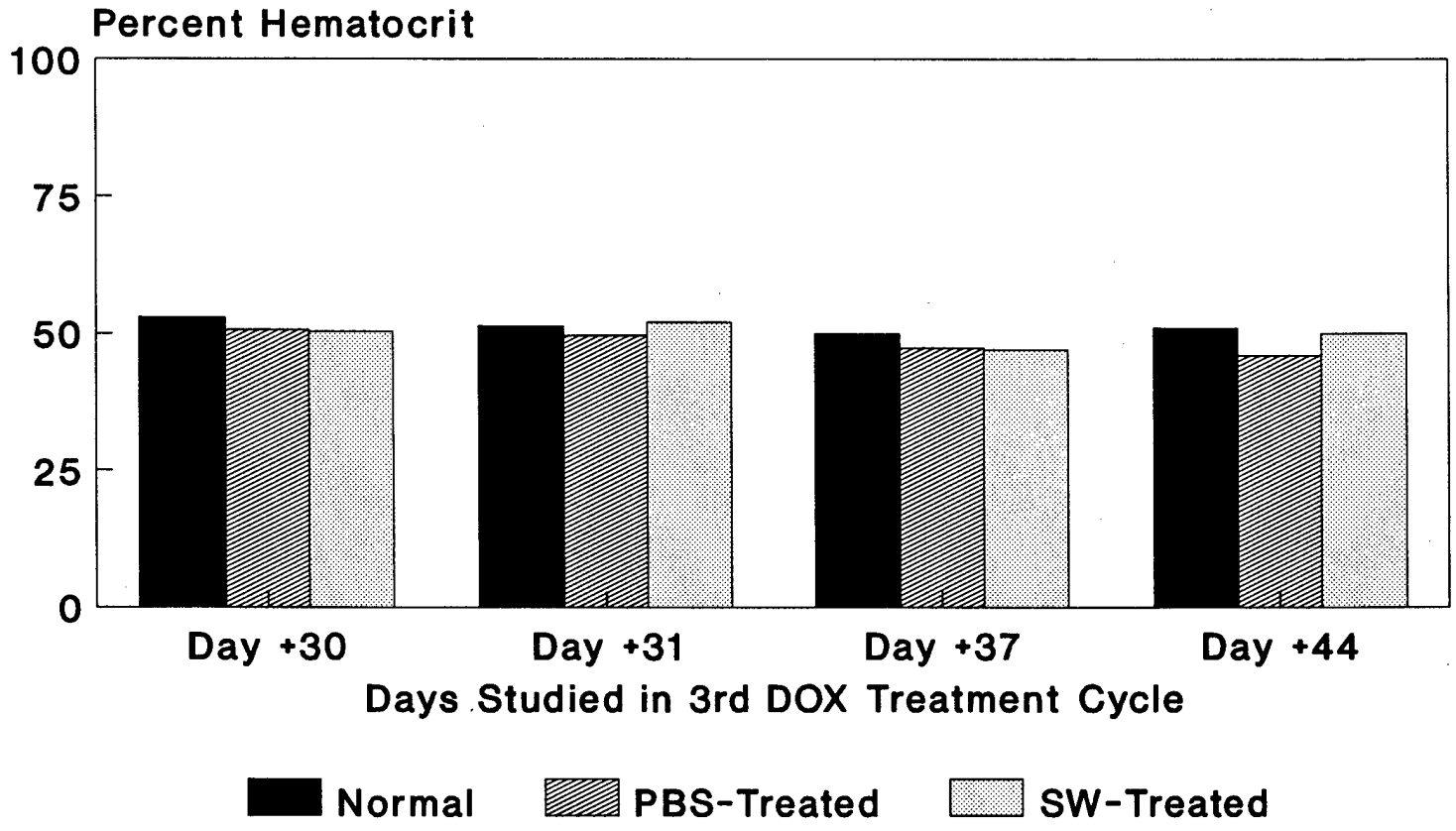

Figure 4N - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on Percent Hematocrit During Intensive High-Dose Chemotherapy

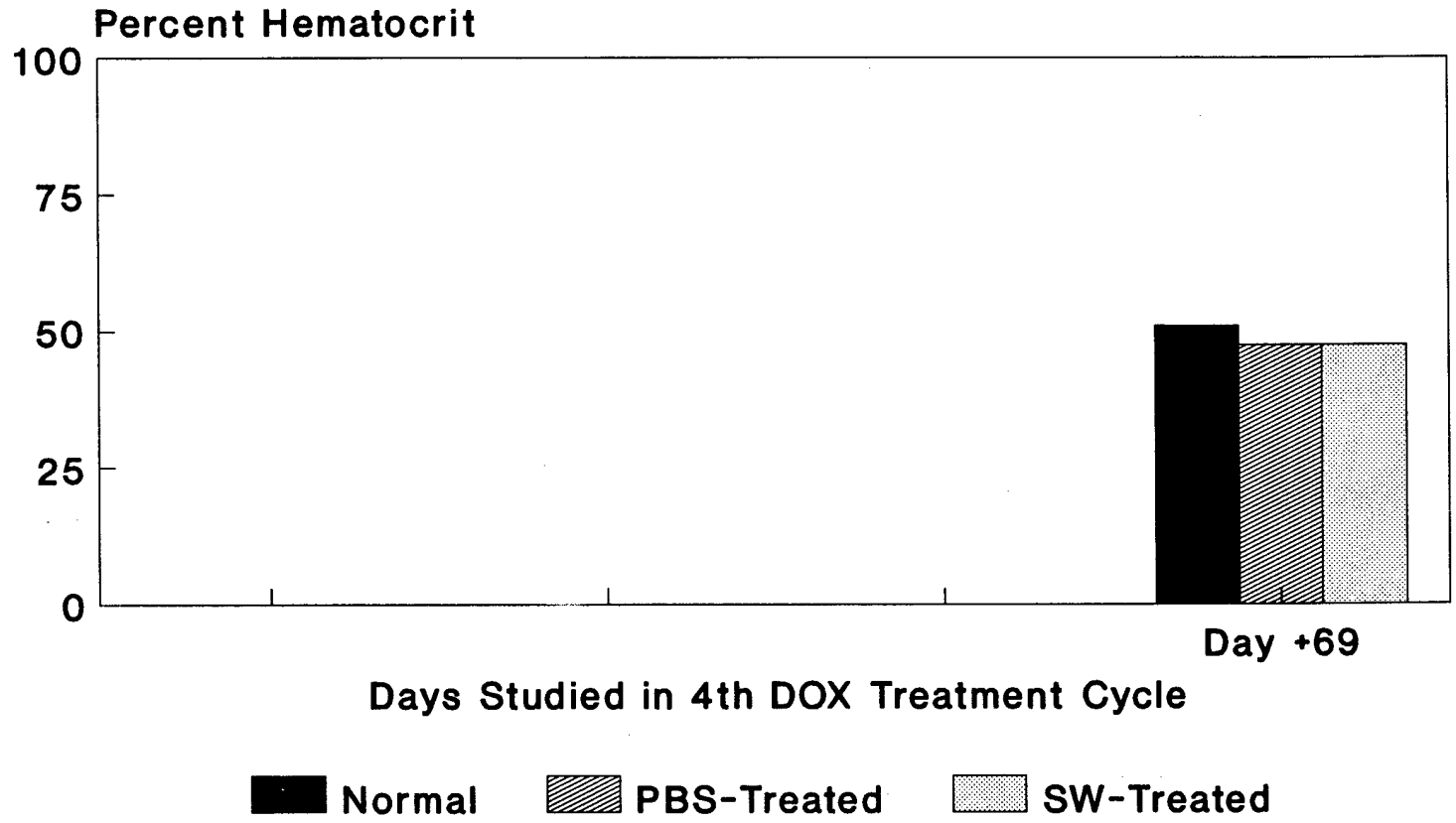

Figure 4O - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on Total CFUs of BM Cells During Intensive High-Dose Chemotherapy

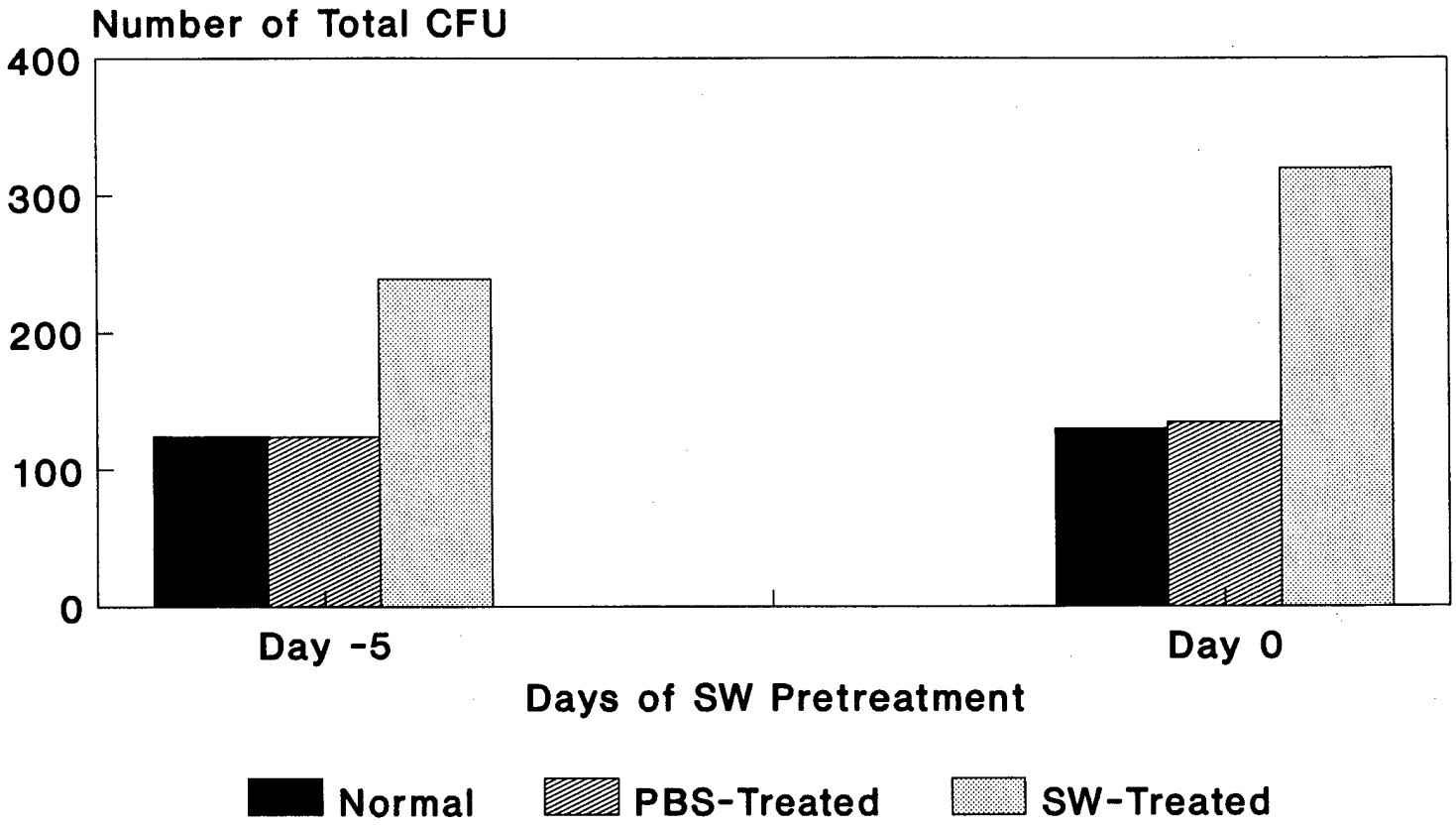

Figure 4P - Effects of SW Pretreatment
on Total CFU of Bone Marrow Cells
CFU = Colony Forming Units

Survival of Mice During Chemotherapy

Effects of SW on BM Total CFU During Intensive High-Dose Chemotherapy

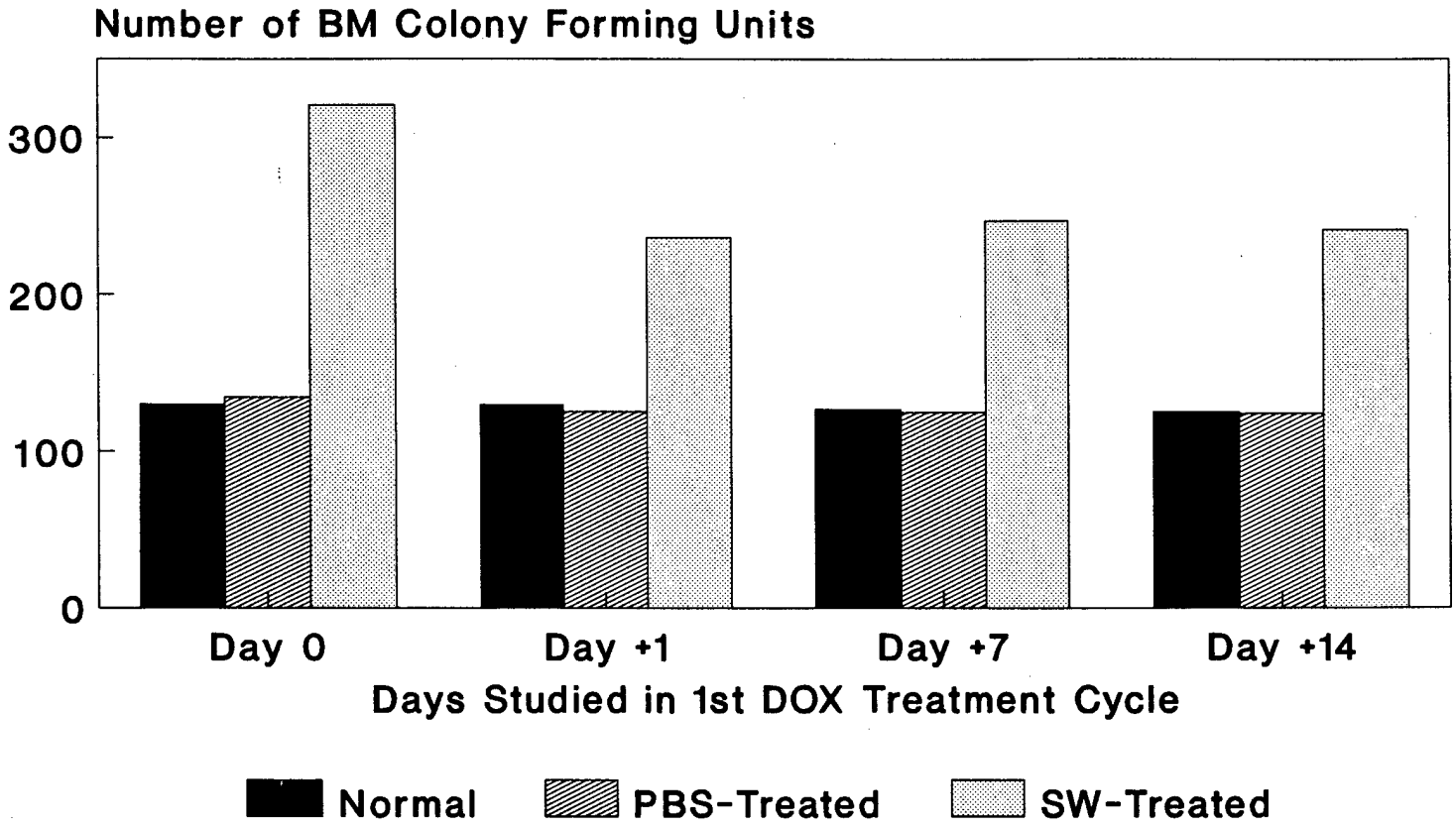

Figure 4Q - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on BM Total CFU During Intensive High-Dose Chemotherapy

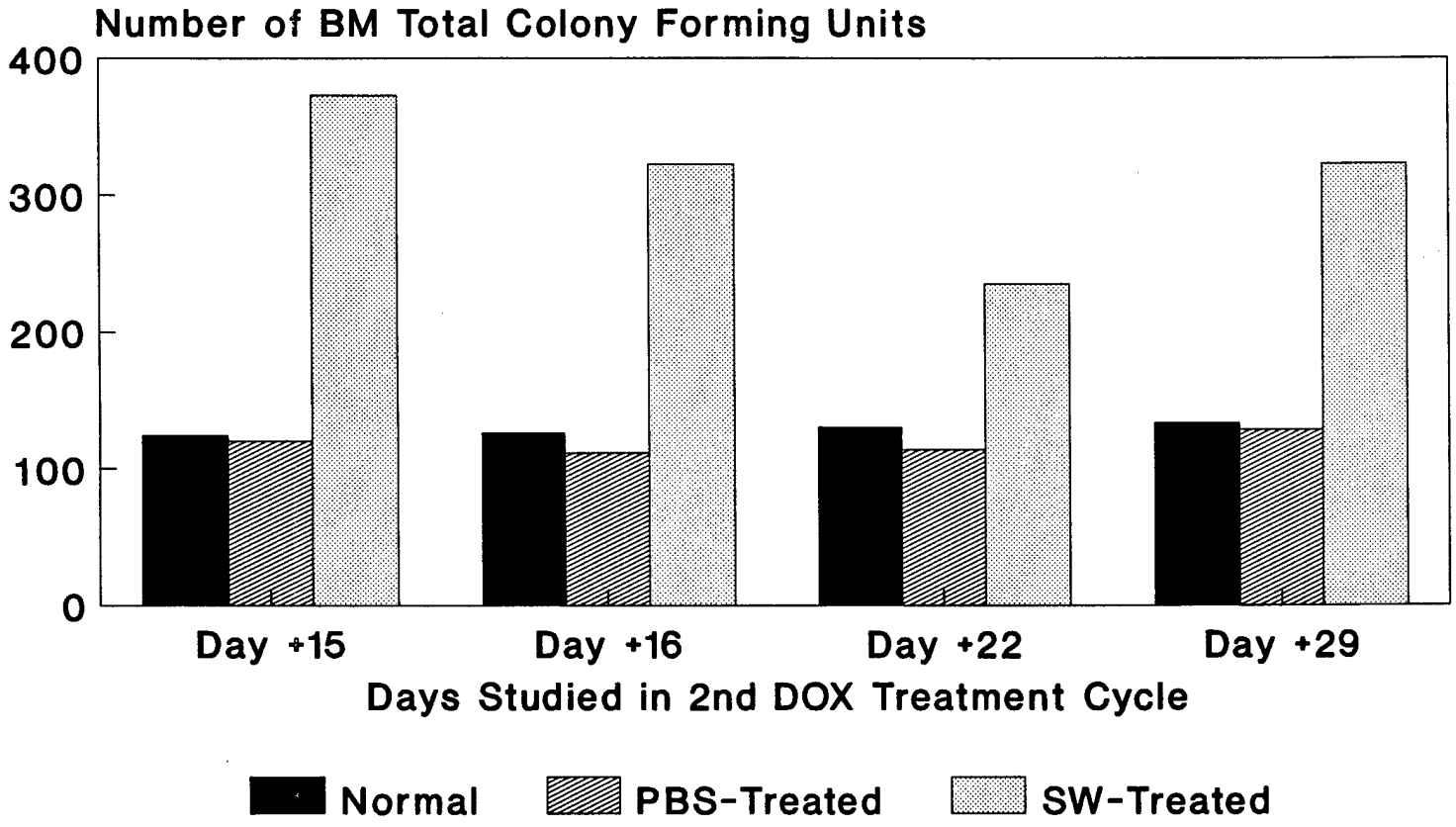

Figure 4R - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on BM Total CFU During Intensive High-Dose Chemotherapy

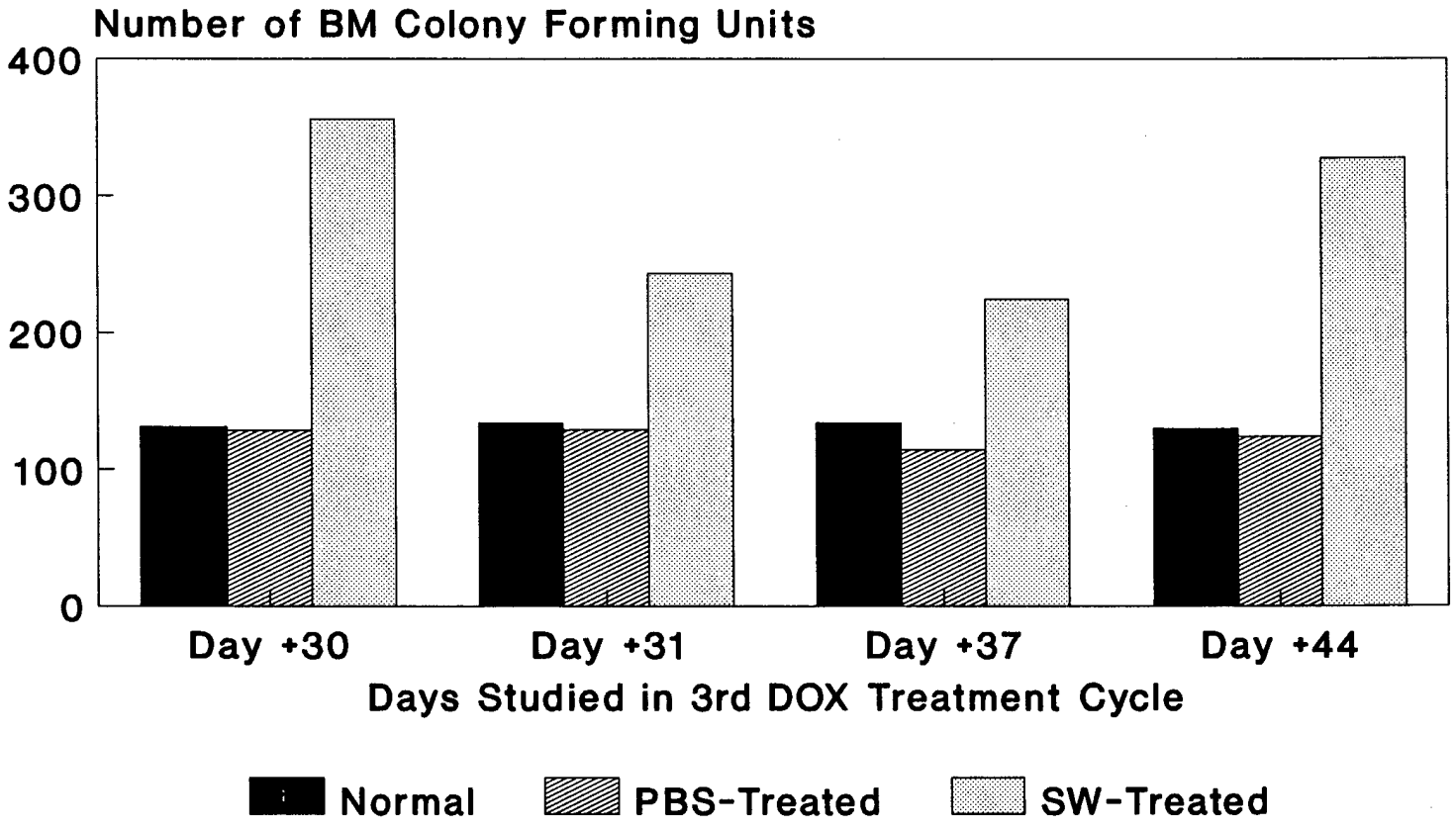

Figure 4S - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on BM Total CFU During Intensive High-Dose Chemotherapy

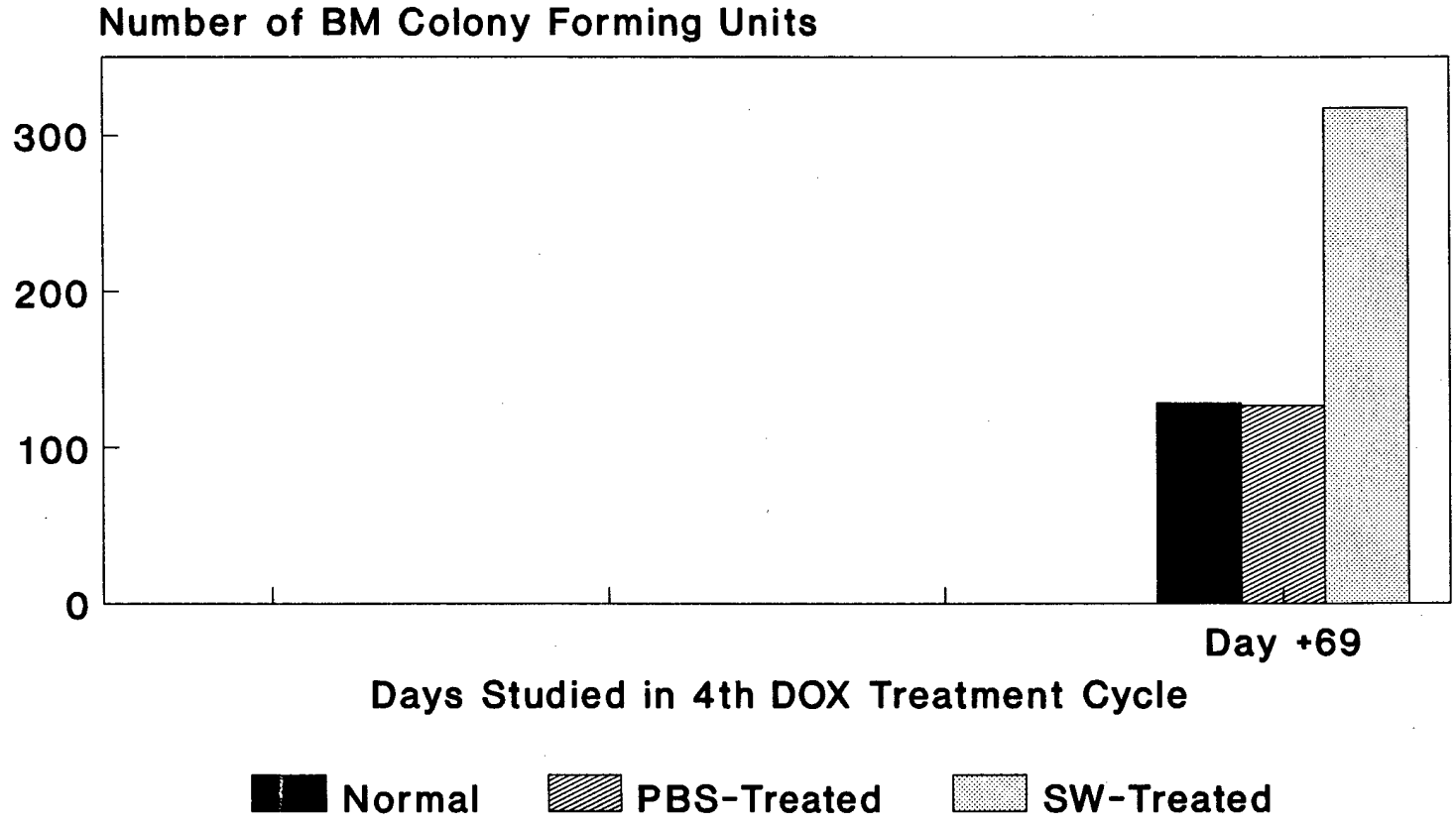

Figure 4T - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on CFU - GM of BM Cells During Intensive High-Dose Chemotherapy

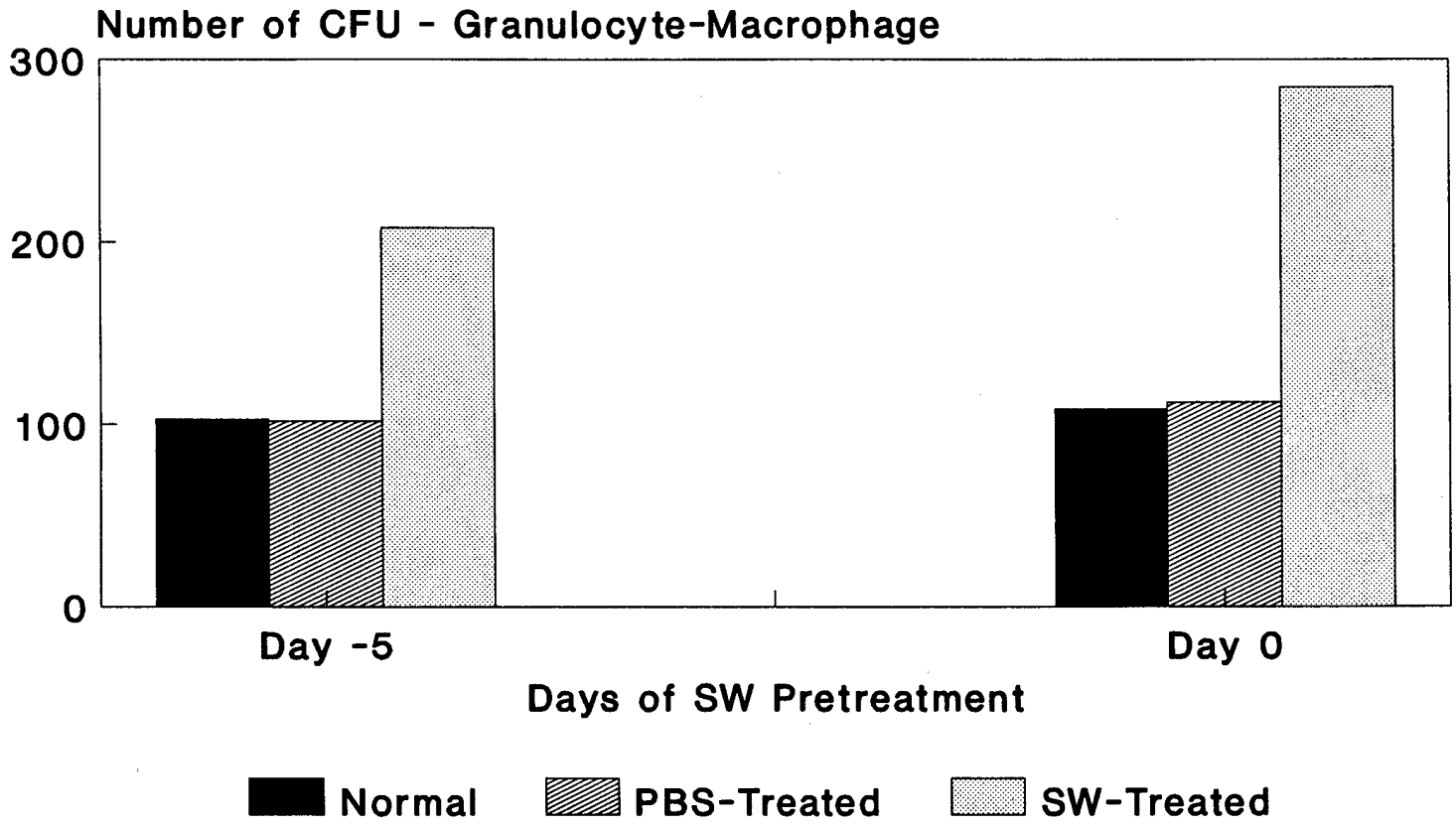

Figure 4U - Effects of SW Pretreatment
on Granulocyte-Macrophage - CFU
CFU = Colony Forming Units

Survival of Mice During Chemotherapy

Effects of SW on CFU - GM of BM Cells During Intensive High-Dose Chemotherapy

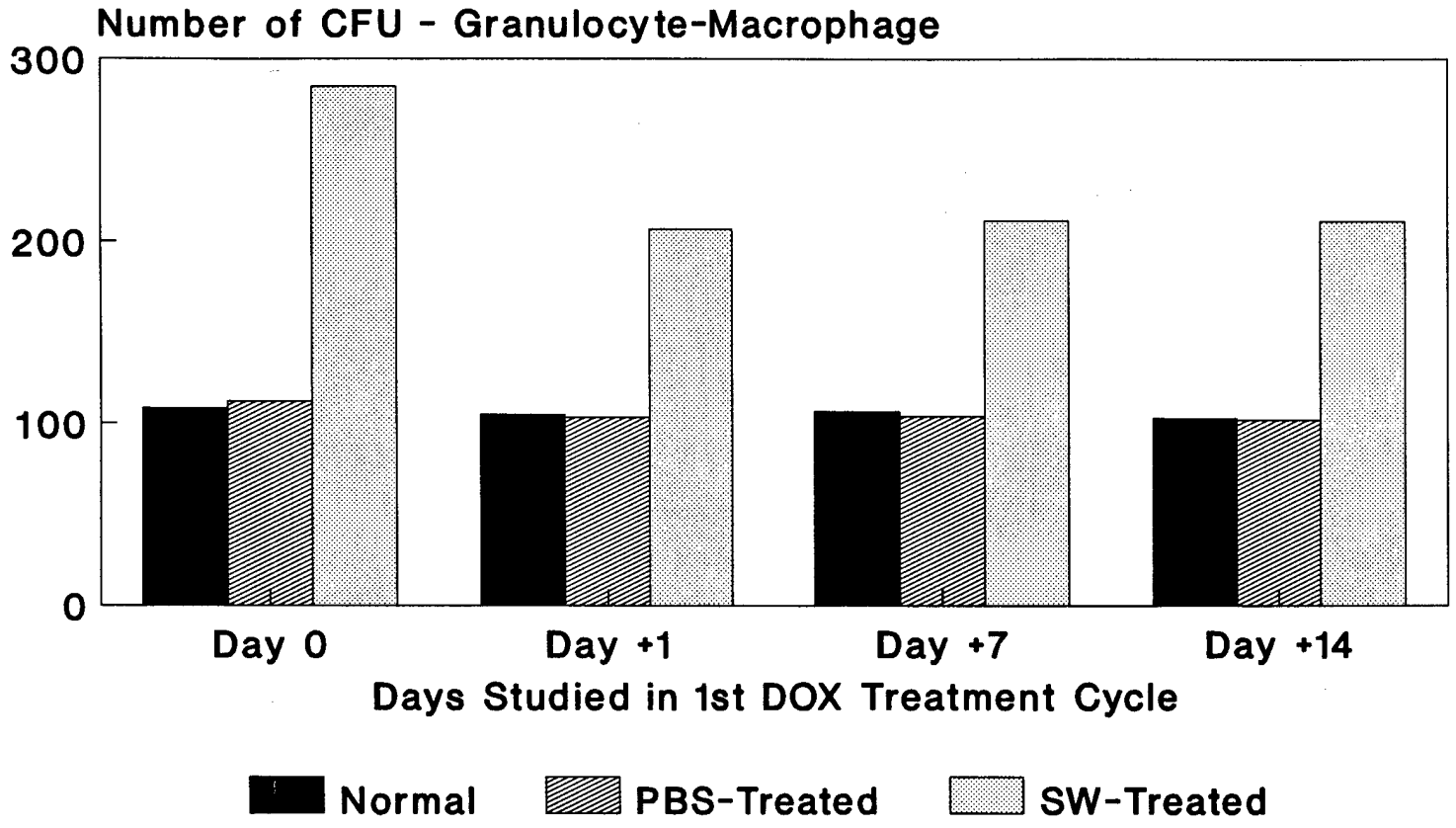

Figure 4V - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on CFU - GM of BM Cells During Intensive High-Dose Chemotherapy

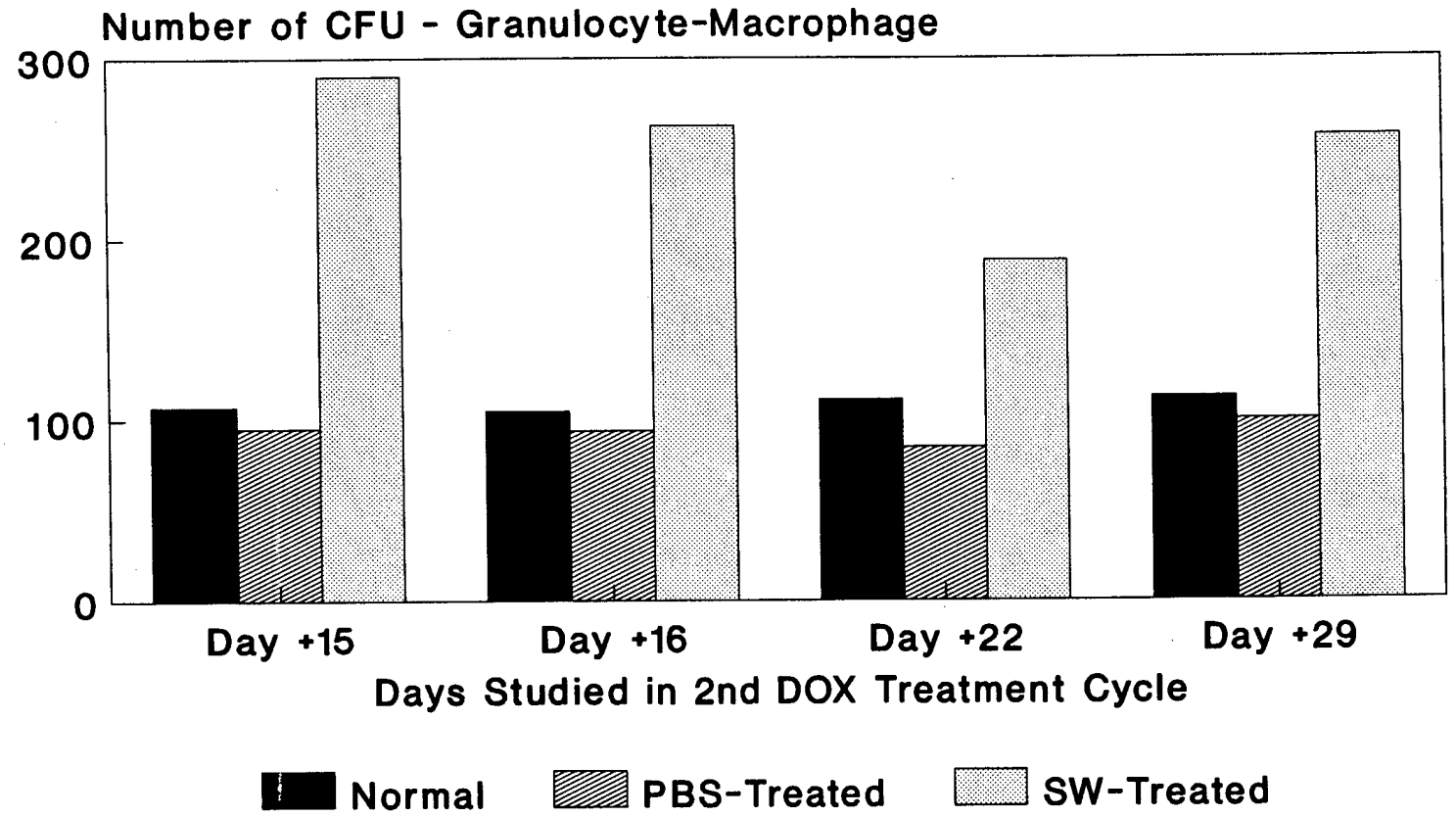

Figure 4W - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on CFU - GM of BM Cells During Intensive High-Dose Chemotherapy

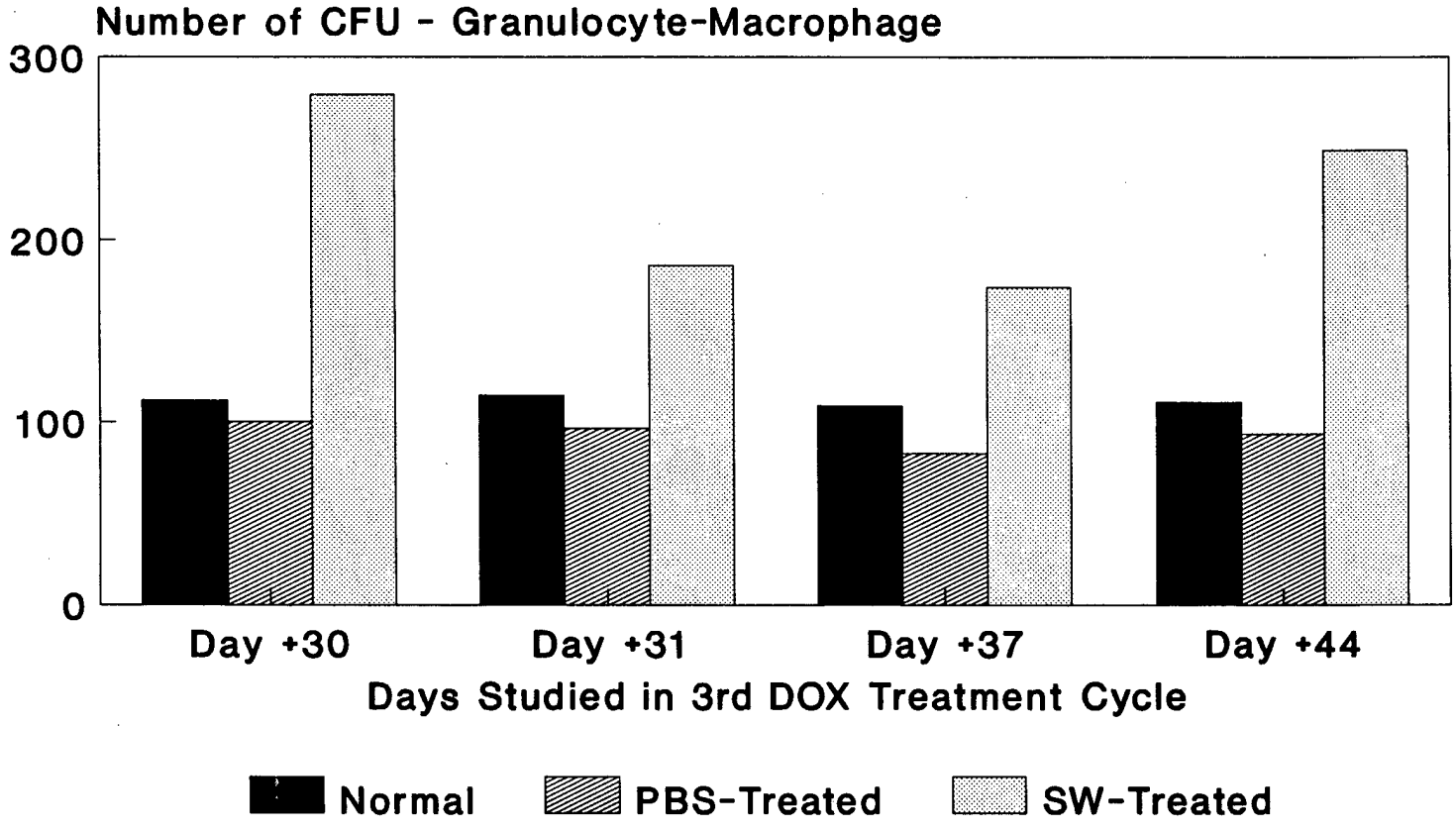

Figure 4X - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on CFU - GM of BM Cells During Intensive High-Dose Chemotherapy

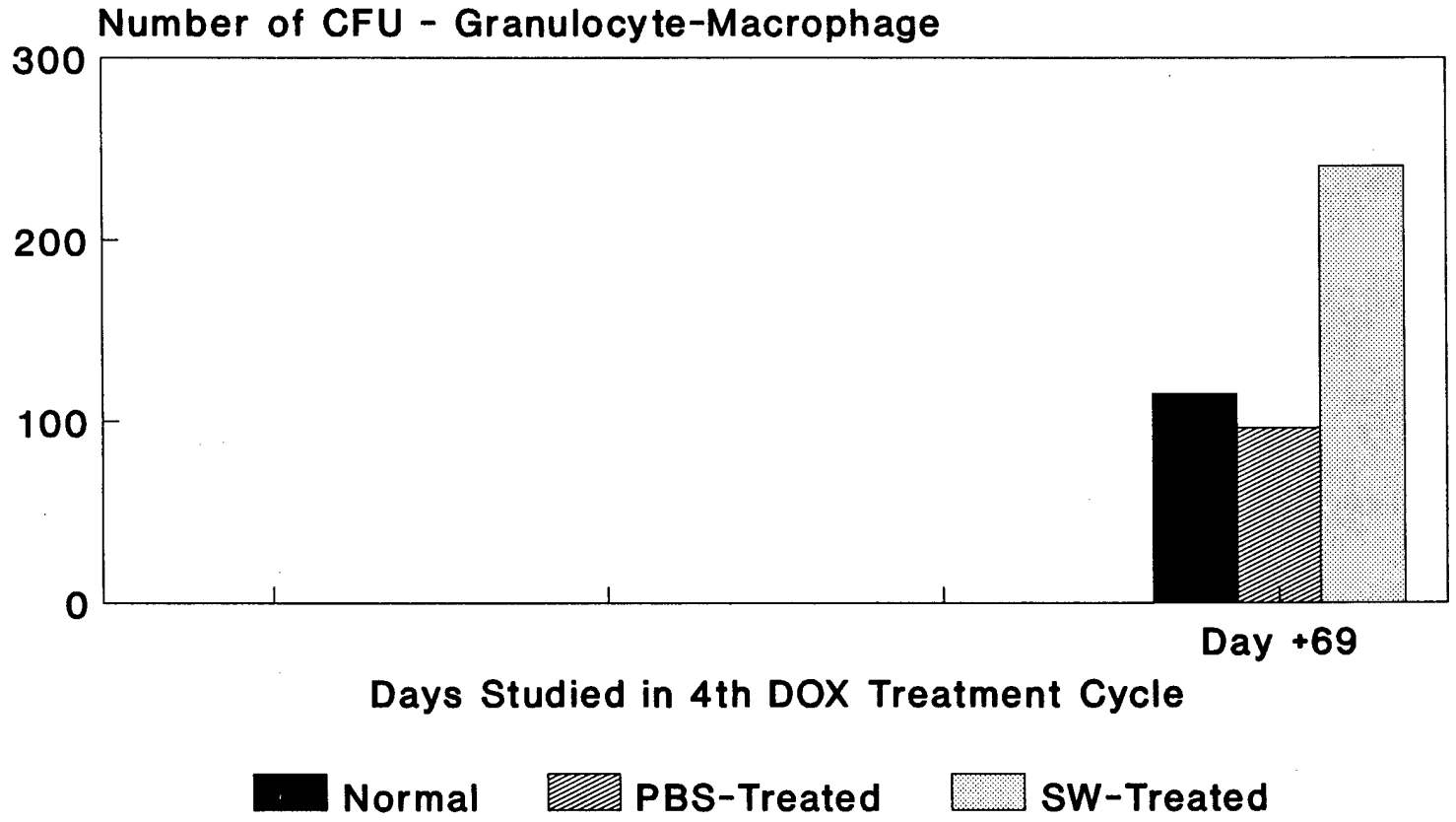

Figure 4Y - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on Burst Erythroid of BM During Intensive High-Dose Chemotherapy

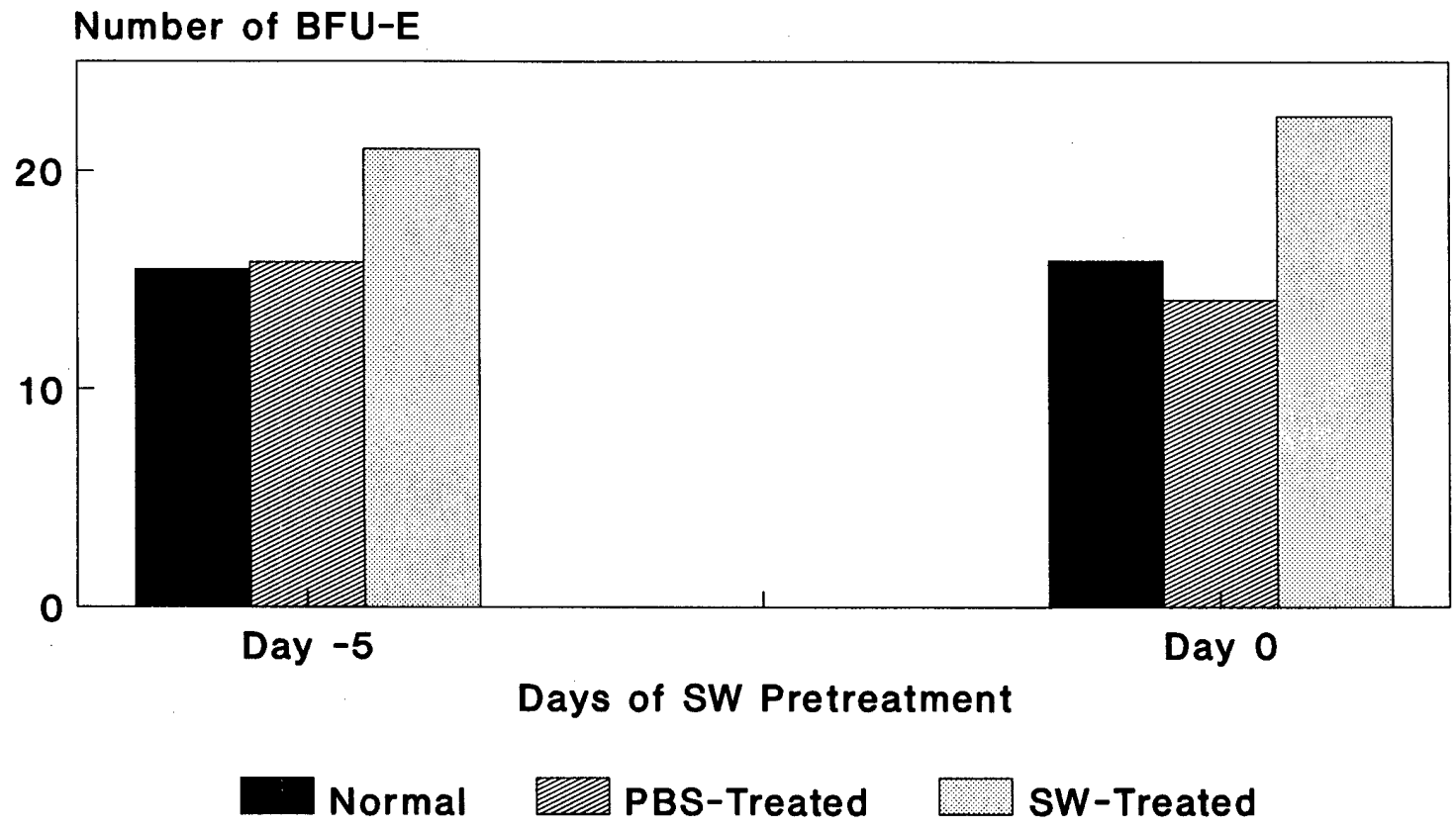

Figure 4Z - Effects of SW Pretreatment on BFU-E
BFU-E = Burst Forming Units-Erythroid

Survival of Mice During Chemotherapy

Effects of SW on BM Burst Erythroid During Intensive High-Dose Chemotherapy

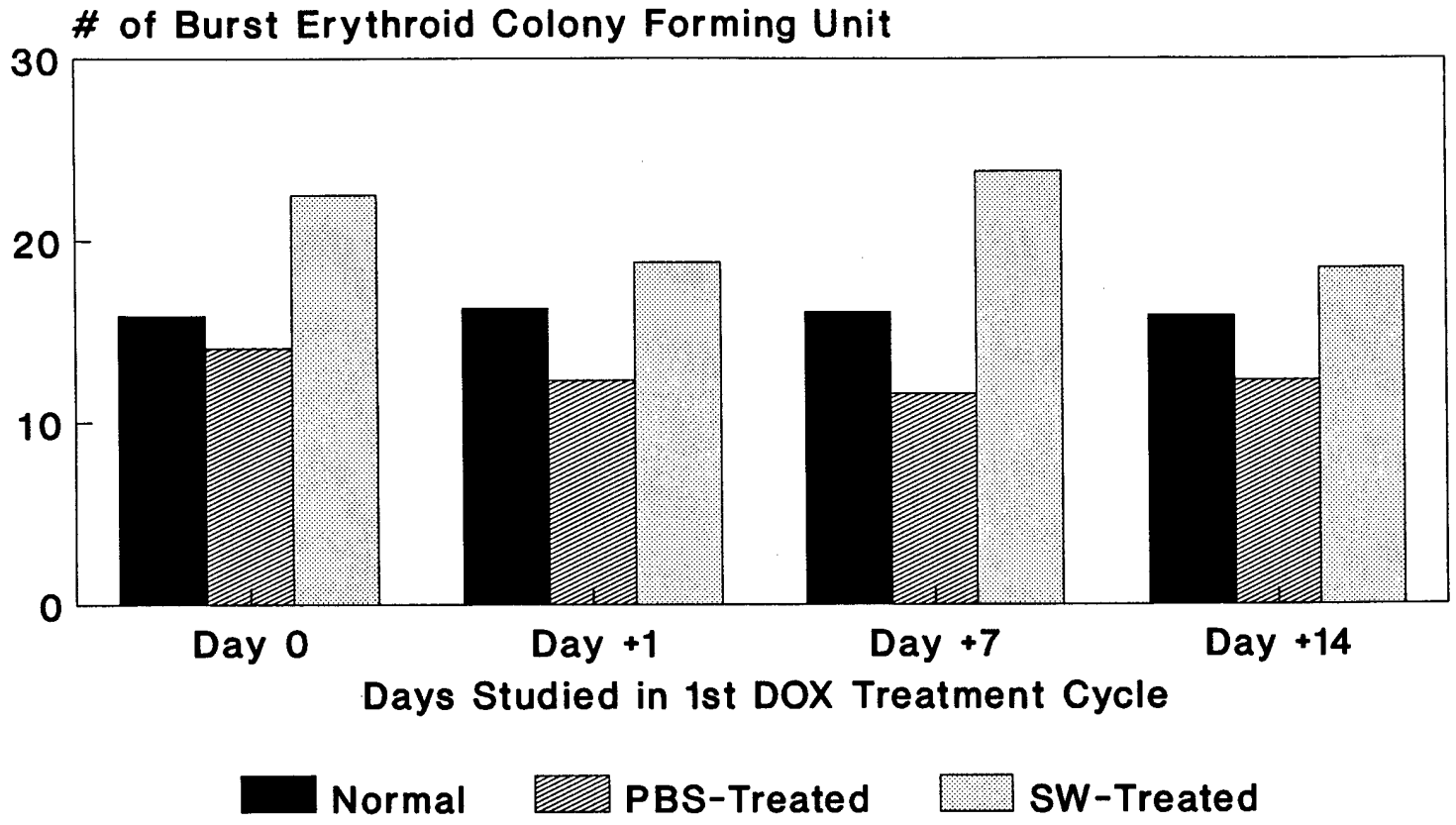

Figure 5A - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on BM Burst Erythroid During Intensive High-Dose Chemotherapy

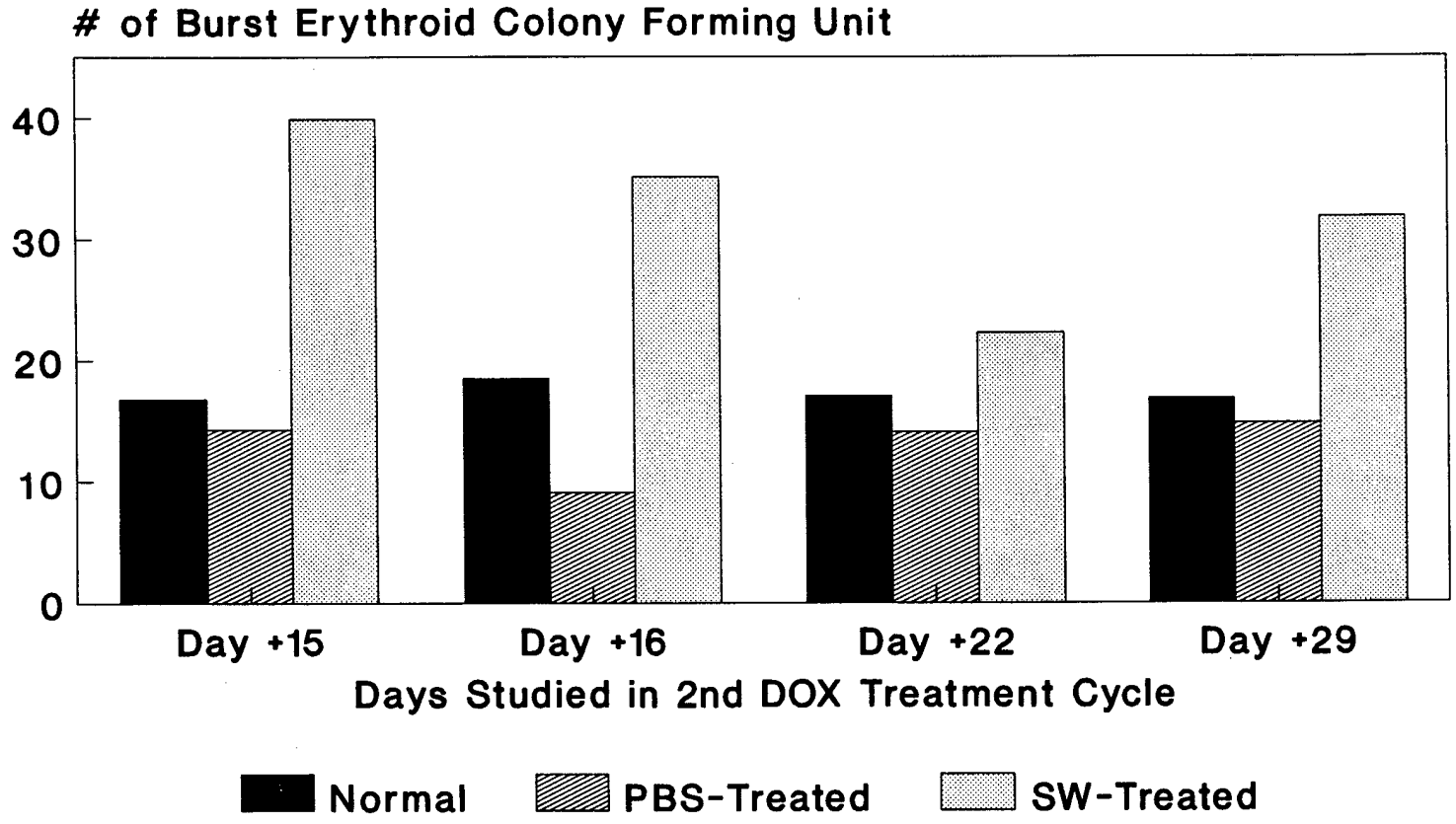

Figure 5B - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on BM Burst Erythroid During Intensive High-Dose Chemotherapy

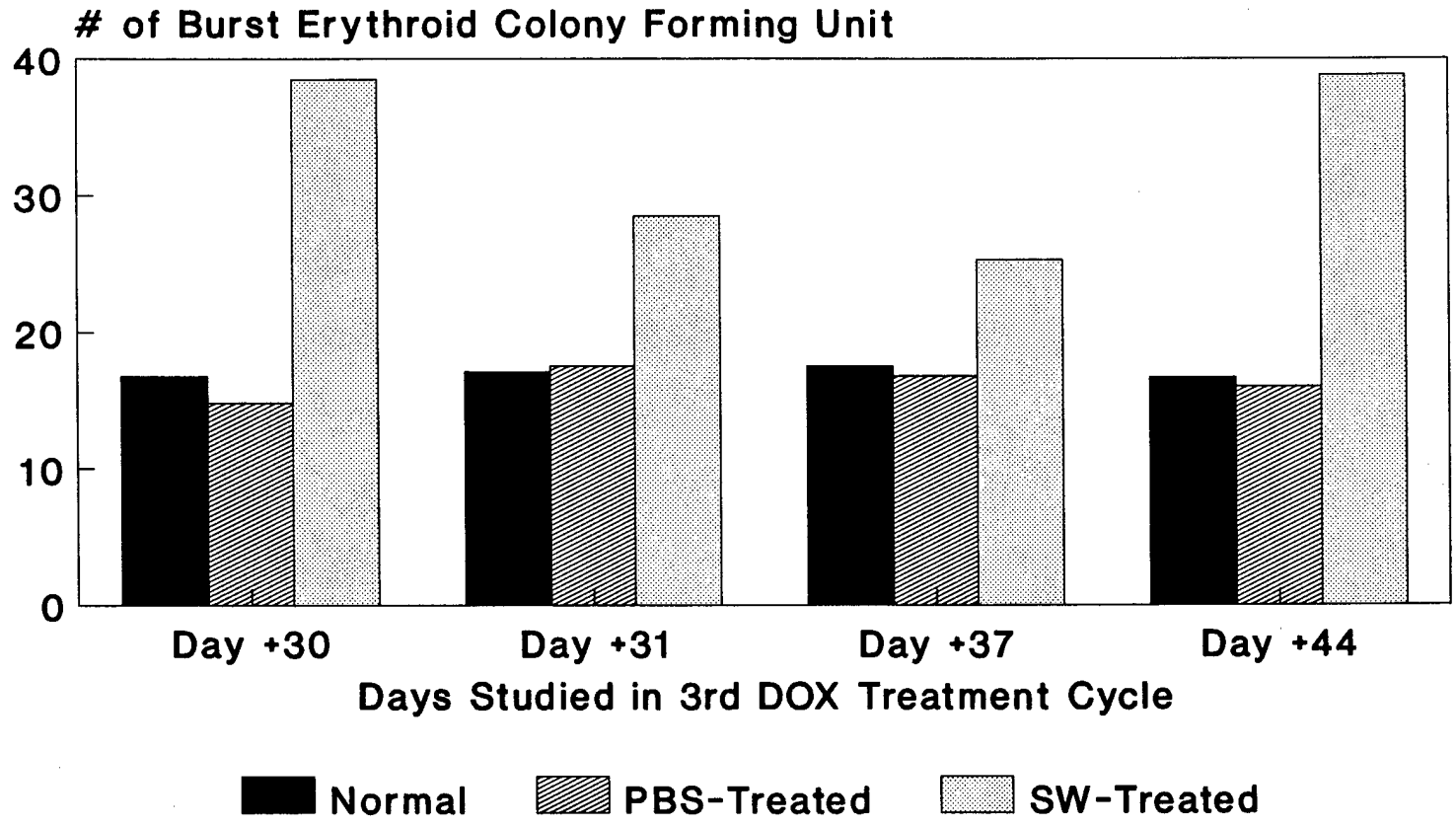

Figure 5C - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on BM Burst Erythroid During Intensive High-Dose Chemotherapy

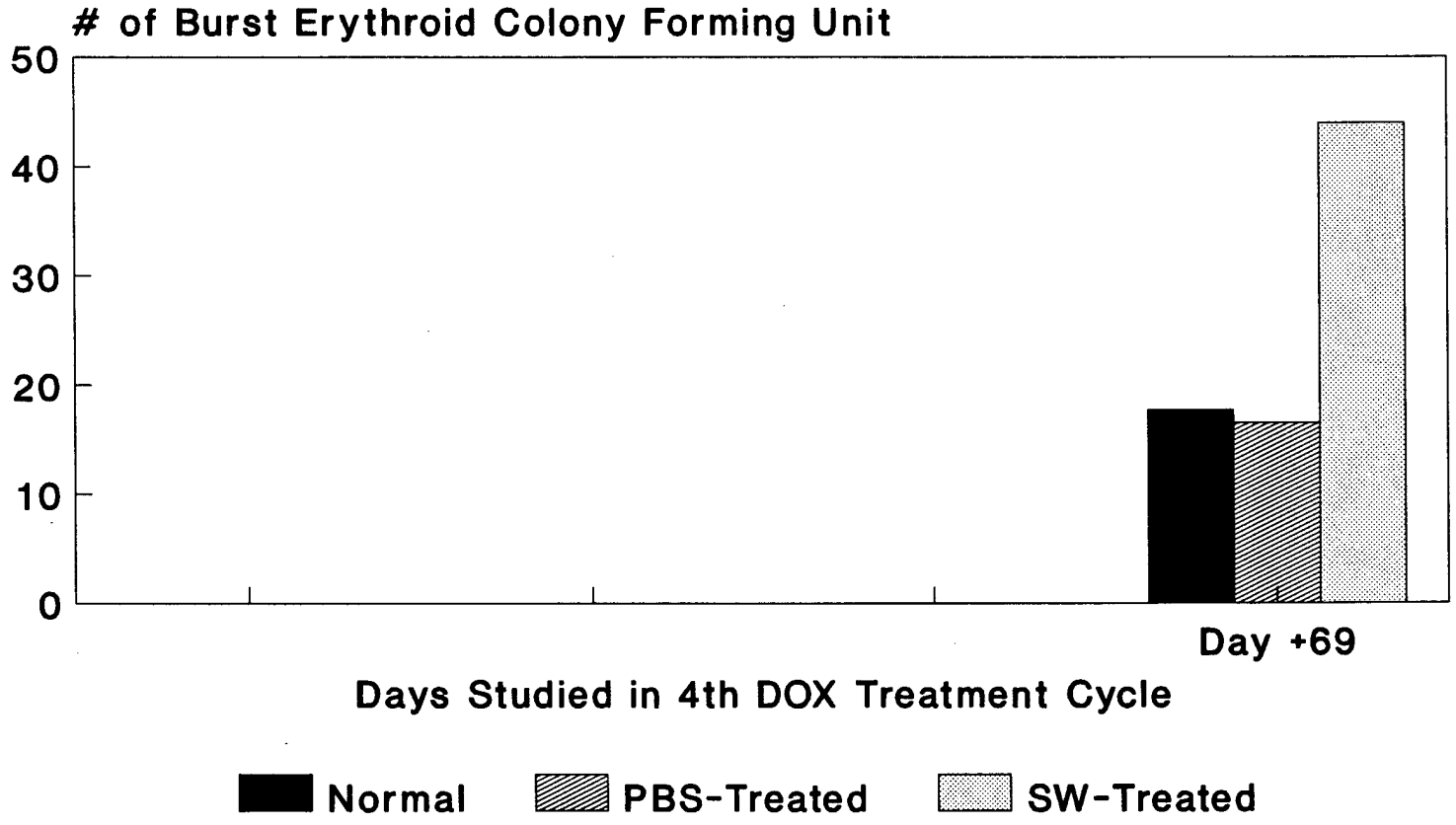

Figure 5D - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on BM CFU - GEMM (Mixed) During Intensive High-Dose Chemotherapy

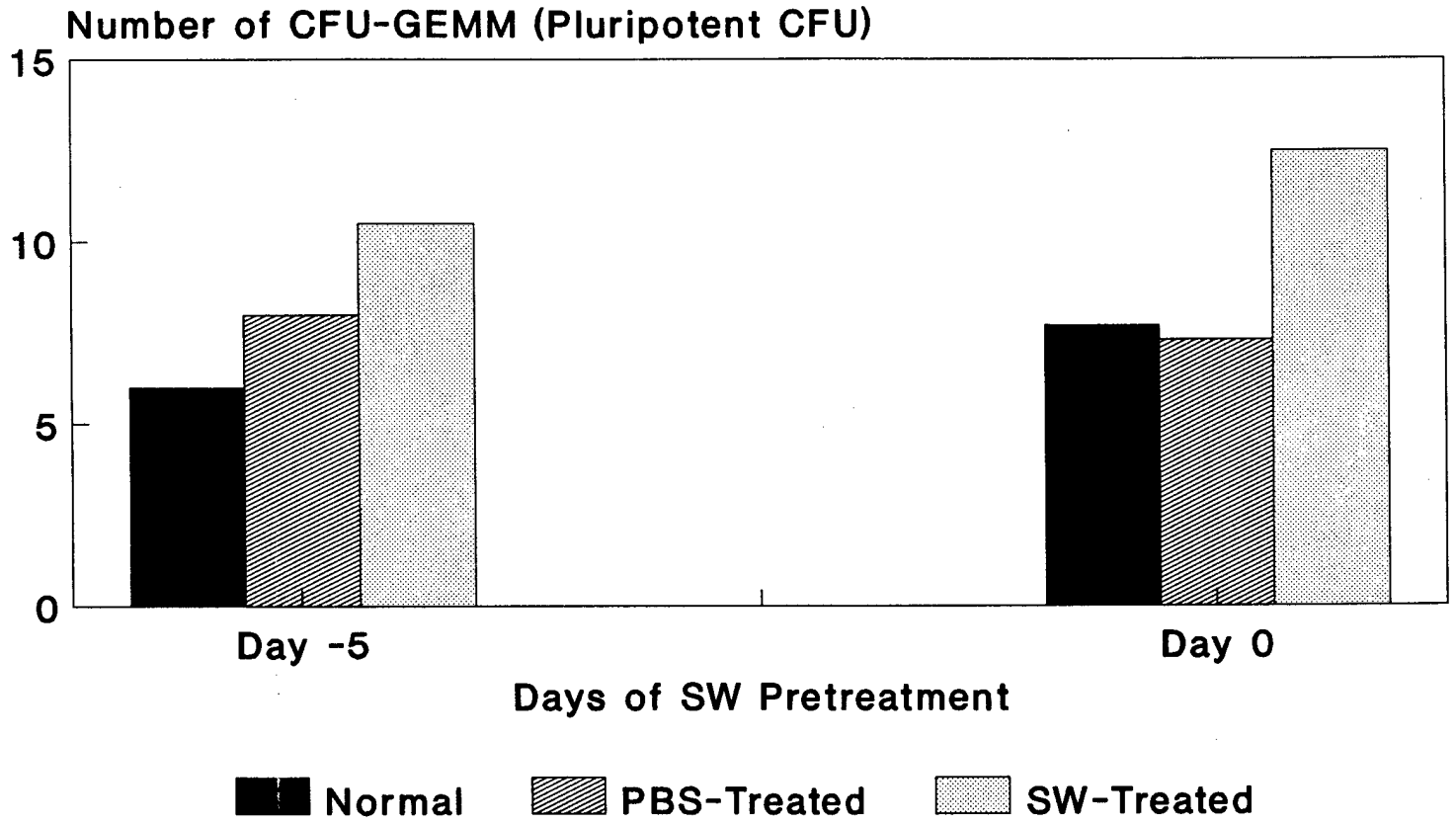

Figure 5E - Effects of SW Pretreatment on CFU-Mixed. CFU-Mixed=CFU-Granulocyte-Erythrocyte-Monocyte-Megakaryocyte

Survival of Mice During Chemotherapy

Effects of SW on BM CFU-GEMM (Mixed) During Intensive High-Dose Chemotherapy

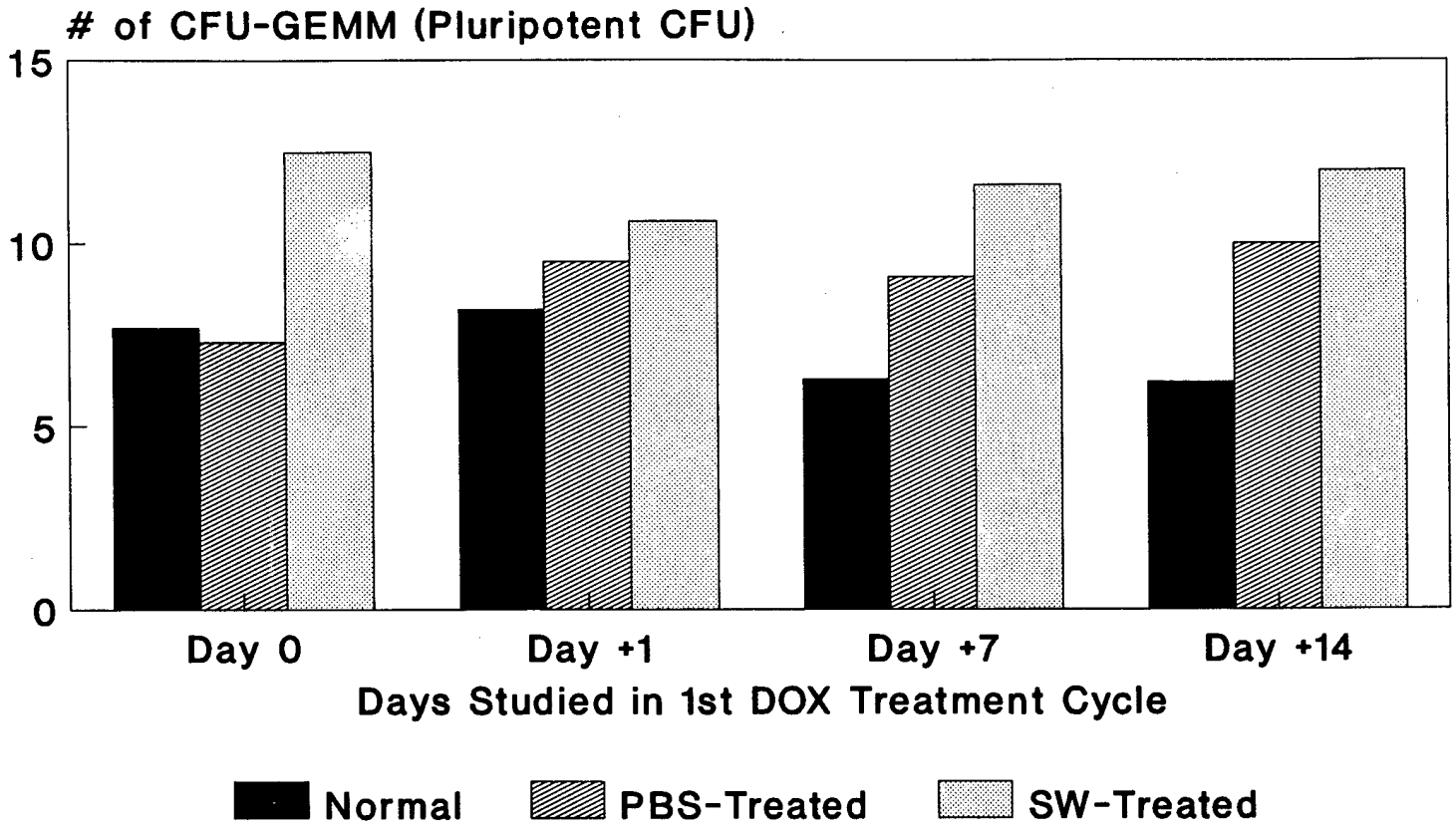

Figure 5F - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on BM CFU-GEMM (Mixed) During Intensive High-Dose Chemotherapy

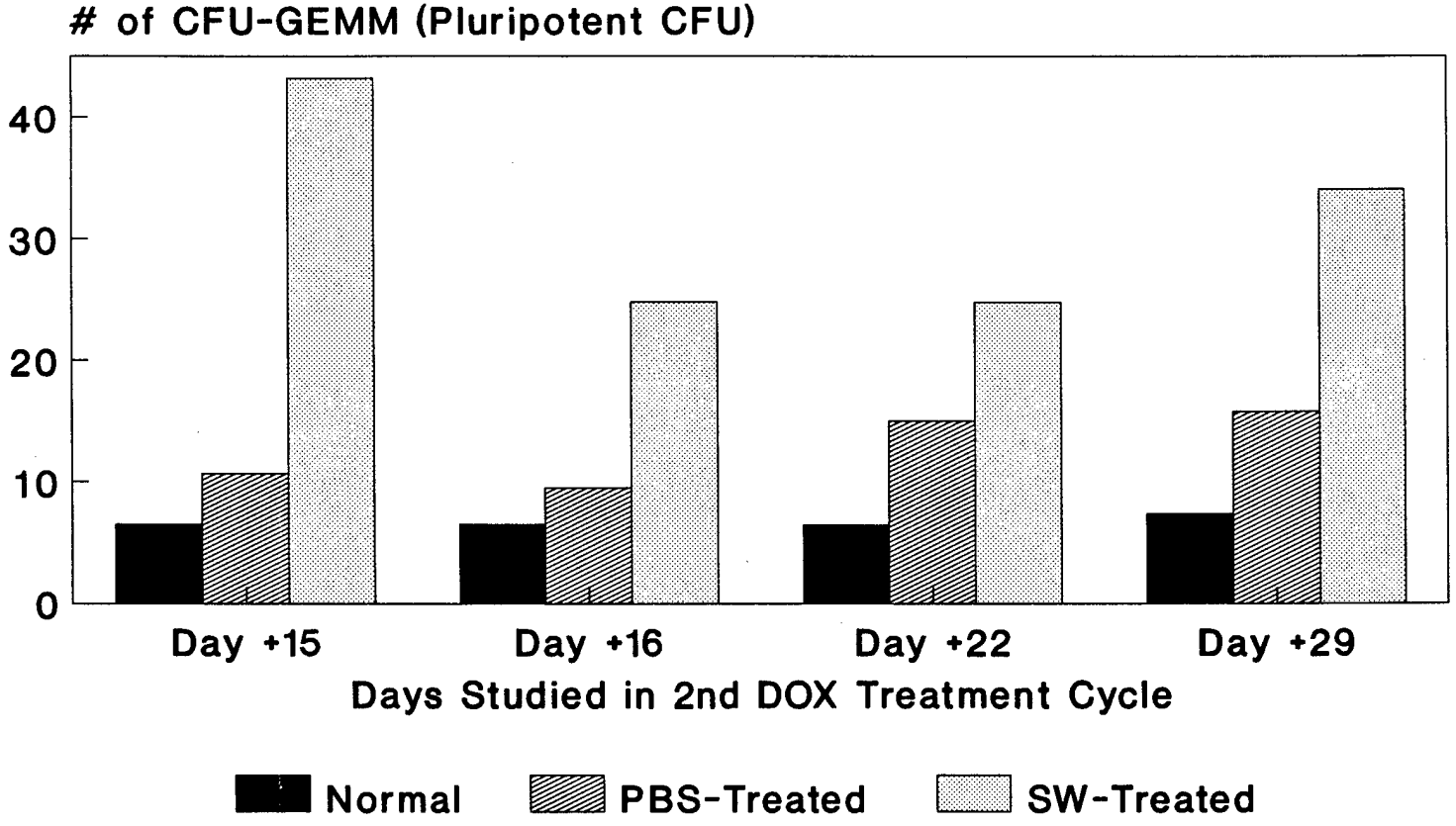

Figure 5G - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on BM CFU-GEMM (Mixed) During Intensive High-Dose Chemotherapy

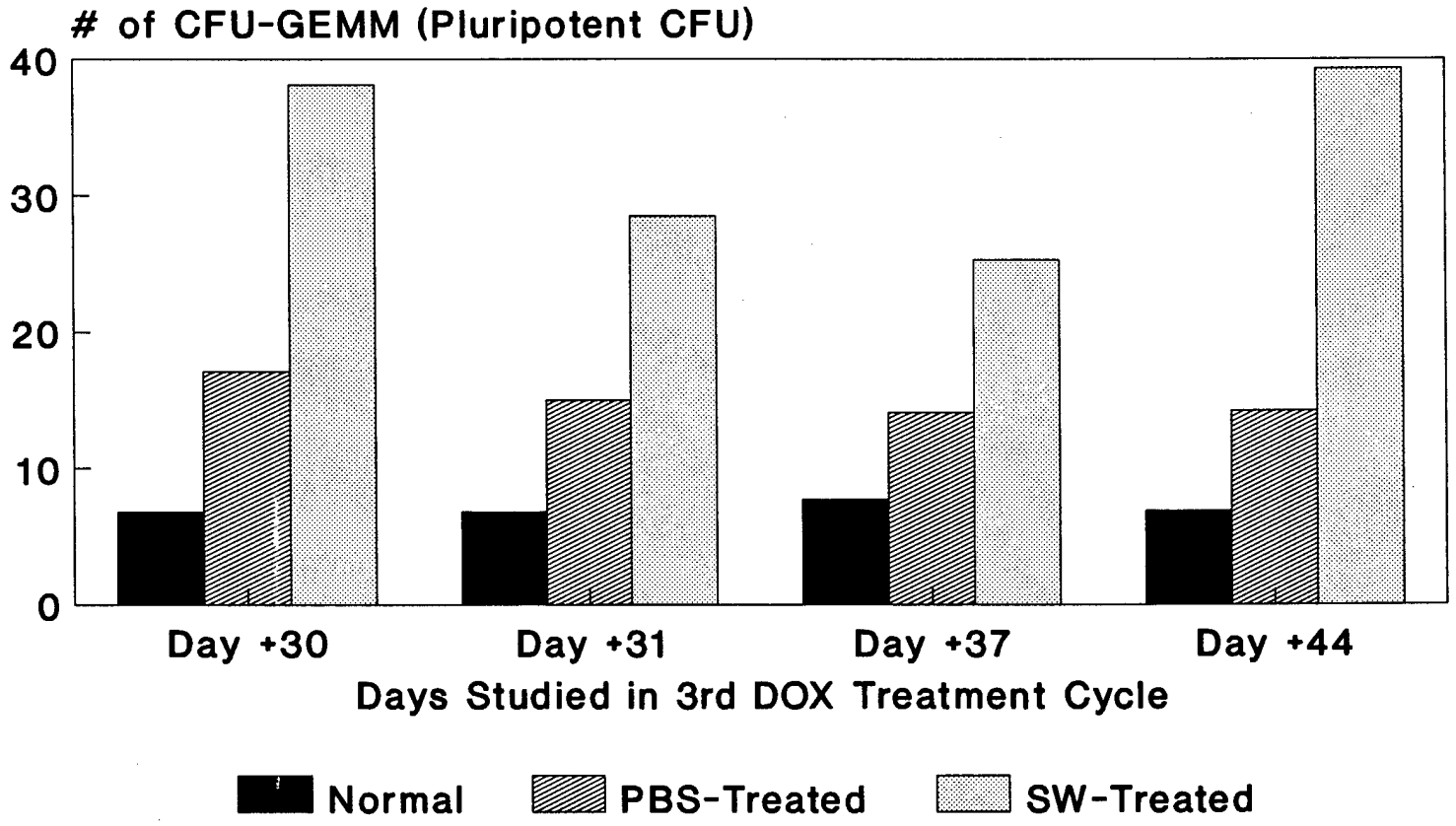

Figure 5H - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54

Survival of Mice During Chemotherapy

Effects of SW on BM CFU-GEMM (Mixed) During Intensive High-Dose Chemotherapy

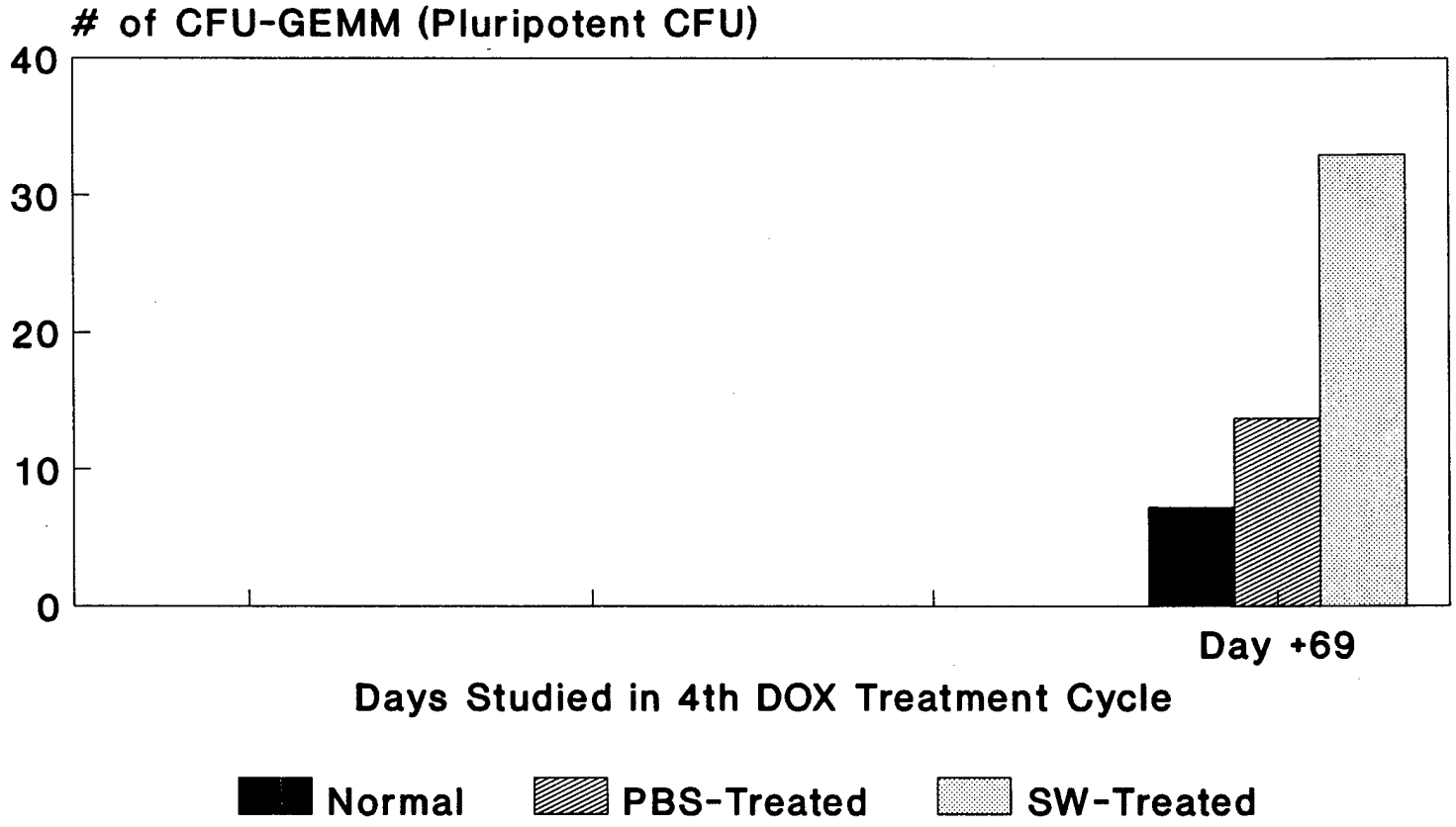

Figure 5l - SW/PBS PreRx from Day -10 to Day 0; LD10 DOX was injected on Day 0, Day+15, Day+30 and Day+55;SW/PBS-D+45-54